ATSDR Agency for Toxic Substances and Disease Registry

Community Assistance Panel (CAP) Meetings

The Agency for Toxic Substances and Disease Registry (ATSDR) has created a community assistance panel (CAP) for the Camp Lejeune site. The purpose of the CAP is to voice the concerns of the affected community of Marines and their families and to provide input on ATSDR's public health activities. The CAP consists of community members, one representative from the Department of Defense (DoD), independent scientific experts, and ATSDR staff. Members of the CAP will provide individual input as well as represent the views of the community and groups to which they belong. ATSDR will consider the views expressed by CAP members during decision making.

The next meeting will be held **April 12, 2017 from 9:00 A.M. to 3:00 P.M.** in Atlanta at the offices of NCEH/ATSDR, located at 4770 Buford Highway, Atlanta, GA. The meeting will be open to the public, but **pre-registration is required to gain entrance into the building. Registration closes on March 28, 2017**. Advance notice of ten working days is required by our security office.

Registration has now closed. **All audience members must arrive at the visitor center by 8:30 A.M. so they can be escorted to the meeting room. Please note that all visitors must have a valid U.S. driver's license or passport to obtain entrance into the building.**

A link for viewing the meeting will be available on the day of the meeting. You do not need to register to view the meeting over the internet.

Camp Lejeune Community Assistance Panel and Agency for Toxic Substances and Disease Registry: General Charter Procedures [PDF - 1.8MB] - March 2016

New! January 21, 2017

Transcript [PDF, 421 KB]

August 11, 2016

Transcript [PDF, 879 KB]

March 24, 2016

Transcript [PDF, 660 KB]

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Page last reviewed: January 16, 2014

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Content source: Agency for Toxic Substances and Disease Registry (/)

ATSDR Agency for Toxic Substances and Disease Registry

Summary of the water contamination situation at Camp Lejeune

- 8 water treatment plants serving the base
  - **Hadnot Point** (HP)
    - Began operation in 1942
    - Areas served:
      - Mainside barracks
      - Hospital Point family housing
      - Family housing at Midway Park, Paradise Point, and Berkeley Manor until June 1972
    - **Tarawa Terrace** (TT)
      - Began operation in 1952
      - Shut down in March 1987
      - Areas served:
        - Tarawa Terrace family housing
        - Knox trailer park
        - **Holcomb Boulevard** (HB)
          - Began operation in June 1972
          - Areas served:
            - Family housing at Midway Park, Paradise Point, Berkeley Manor, and Watkins Village
            - Tarawa Terrace family housing after March 1987
            - **Courthouse Bay**
            - **Rifle Range**
            - **Onslow Beach**
            - **Montford Point/Camp Johnson**
            - **New River**
            - VOCs detected in HP and TT wells during 1980-85 sampling program
            - Samples collected by Camp Lejeune staff
            - Chemicals detected included TCE, PCE, benzene, DCE
            - Contamination of wells began many years before detection
            - Other on-base treatment plants were not contaminated
        - Contamination of HP and TT drinking water systems was intermittent

  - Wells rotated in and out of service
  - Each system had more wells than necessary to supply water on any given day
- **Tarawa Terrace Treatment Plant**
- PCE (perchloroethylene or tetrachloroethylene) was the main contaminant
- Maximum level detected in drinking water was 215 parts per billion (ppb) in February 1985
- Source of contamination was ABC One-Hour Cleaners, an off-base dry cleaning firm
- The most contaminated wells were shut down in February 1985
- ATSDR used water modeling to estimate past exposure levels
- PCE concentration exceeded the current EPA maximum contaminant level of 5 ppb in drinking water for 346 months during November 1957-February 1987
- **Hadnot Point Treatment Plant**
- TCE (trichloroethylene) was the main contaminant
- Maximum level detected in drinking water was 1,400 ppb in May 1982
  - The current limit for TCE in drinking water is 5 ppb
- Other contaminants detected included PCE, DCE, vinyl chloride and benzene
- Multiple sources of contamination
  - Leaking underground storage tanks
  - Waste disposal sites
- The most contaminated wells were shut down by February 1985
- ATSDR used water modeling to estimate past exposure levels
  - At least one VOC exceeded its current EPA maximum contaminant level in drinking water during August 1953 and January 1985

- **Holcomb Boulevard** (HB) wells were generally not contaminated
- Contaminated water from the Hadnot Point (HP) water treatment plant supplied the HB drinking-water system when the HB plant was shut down during January 27-Febraury 7, 1985
- Contaminated water from HP water treatment plant was used intermittently to supplement the HB drinking-water supply during dry spring and summer months when demand was high

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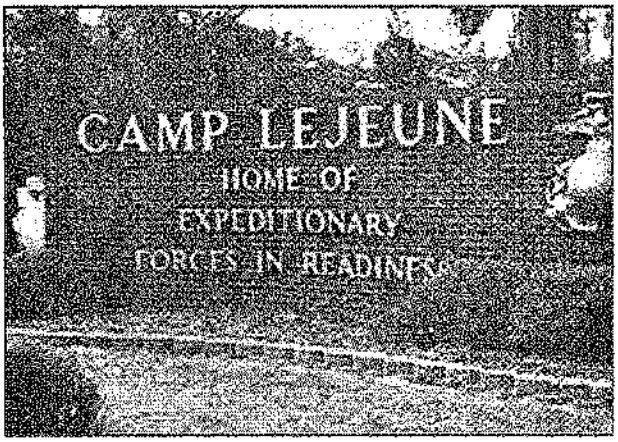
ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases



January 13, 2017

ATSDR
AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY

ATSDR Assessment of the Evidence for the Drinking Water Contaminants at Camp Lejeune and Specific Cancers and Other Diseases

January 13, 2017

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Overview

The Agency for Toxic Substances and Disease Registry (ATSDR) has a unique mandate under the Superfund laws to assess the presence and nature of health hazards at specific Superfund sites, to help prevent or reduce further exposure and the illnesses that result from such exposures, and to expand the knowledge base about health effects from exposure to hazardous substances. As part of its mandate, ATSDR has completed several epidemiological studies to determine if Marines, Navy personnel and civilians residing and working on U.S. Marine Corps Base Camp Lejeune were at increased risk for certain health effects as a result of exposure to water contaminated with volatile organic compounds (VOCS). These studies, two retrospective cohort mortality studies of Marines/Navy personnel and of civilian workers, and a case-control study of male breast cancer among Marines (Bove et al. 2014a, Bove et al. 2014b, Ruckart et al. 2015), used data from extensive water modeling (Maslia et al. 2007, 2013) to reconstruct monthly levels of contaminants in the drinking water. These contaminants included trichloroethylene (TCE), tetrachloroethylene (PCE), benzene, 1,2-dichloroethylene (DCE) and vinyl chloride. The two cohort studies found elevated risks for several cancers, including cancers of the kidney, rectum, prostate, lung, leukemias and multiple myeloma, when compared to similar unexposed cohorts from U.S. Marine Corps Base Camp Pendleton. Parkinson disease was elevated among civilian workers at Camp Lejeune but could not be evaluated in the study of Marines/Navy personnel due to small numbers. Findings from the case-control study suggested possible associations between male breast cancer and being stationed at Camp Lejeune and cumulative exposure to the contaminated drinking water but the study was limited by the small number of cases in the higher exposure categories.

ATSDR integrated the findings from its Camp Lejeune studies with findings from studies of other populations exposed occupationally or environmentally to the chemicals detected in the drinking water at Camp Lejeune: trichloroethylene (TCE), tetrachloroethylene (also known as perchloroethylene or PCE), vinyl chloride and benzene. The purpose was to assess the strength of the evidence supporting causality of adverse health effects from exposures to the drinking water contaminants at Camp Lejeune. This report represents ATSDR's assessment of the state of evidence at this time.

For this assessment, ATSDR did not conduct any new meta-analyses. Instead, ATSDR reviewed the scientific literature on these contaminants and placed high weight on assessments conducted by other agencies mandated to evaluate the health effects of these chemicals: i.e., the U.S. Environmental Protection Agency (EPA 2011, 2012), the National Toxicology Program (NTP 2015) and the International Agency for Research on Cancer (IARC 100F, 2012; 106, 2014). High weight was also given to meta-analyses conducted by EPA (Scott and Jinot 2011) and other researchers. This report summarizes the evidence for 16 diseases for which there was at least some epidemiological evidence for an association with either TCE or PCE, the primary contaminants in the drinking water systems at Camp Lejeune. The report also assesses the evidence linking these diseases with vinyl chloride and benzene. **Two additional diseases, lung cancer and cervical cancer, are not included in this report. ATSDR is currently updating its assessment of these two cancers and will publish the assessment at a later date.**

Background

The Hadnot Point treatment plant provided drinking water to the main portion of the base at Camp Lejeune, including most of the barracks and workplaces. Samples of the Hadnot Point distribution system were conducted by the base in May and July 1982, December 1984, and throughout 1985. During the 1982 sampling, measured levels of TCE and PCE in the distribution system of Hadnot Point were as high as 1,400 ppb and 100 ppb, respectively. Vinyl chloride and benzene were also detected in the Hadnot Point distribution system during sampling conducted on or after December 1984. The Tarawa Terrace treatment plant provided drinking water to the Tarawa Terrace housing area at the base. Samples of the Tarawa Terrace distribution system were conducted by the base in May and July 1982, and February 1985 onward. During the July 1982 distribution system sampling, PCE was measured as high as 104 ppb and reached a maximum of 215 ppb during the February 1985 sampling.

The current U.S. maximum contaminant levels (MCLs) for TCE and PCE are 5 ppb. The MCLs for vinyl chloride and benzene are 2 ppb and 5 ppb, respectively. The MCLs for TCE, vinyl chloride and benzene were in effect as of 1989, and the MCL for PCE was in effect as of 1992. Historical reconstruction modeling of the drinking water contamination indicated that TCE and PCE levels above their current MCLs were likely present in the distribution systems since the 1950s. The highly contaminated supply wells serving these systems were shut down by February 1985. For the retrospective cohort study of Marines and Navy personnel at Camp Lejeune, the relevant exposure period was 1975 – January 1985. The estimated monthly average contaminant concentrations in the Hadnot Point and Tarawa Terrace systems during this period are shown in tables in the appendix of this report. In the Hadnot Point system, the median monthly estimated average concentrations of TCE, PCE, vinyl chloride and benzene was 366 ppb, 15 ppb, 22 ppb and 5 ppb, respectively. In the Tarawa Terrace system, the median monthly estimated average concentrations of PCE, TCE and vinyl chloride were 85 ppb, 4 ppb and 6 ppb. The median number of months a marine or Navy personnel was stationed at the base was 18 months.

A marine in training at Camp Lejeune consumes an estimated 6 liters of water per day for three days per week and 3 liters per day the rest of the week (ATSDR 2016). Under warm weather conditions, a marine may consume between 1 and 2 quarts of water per hour and shower twice a day (Bove et al. 2014a). It is likely that during training, the water supplied in the field came from the Hadnot Point water system with both measured and estimated levels of TCE and PCE substantially higher than their MCLs.

Methods

Description of the candidate list of diseases

The selection of diseases for assessment was initially based on a previous review of the literature that was included in a feasibility assessment for the mortality studies at Camp Lejeune (Bove and Ruckart 2008). That literature review identified a list of diseases for which there was at least limited or suggestive evidence of an association with exposures to TCE or PCE. Limited or suggestive evidence was considered to have occurred when a positive association (e.g., an effect estimate such as the relative

risk or the odds ratio is greater than 1.0) was observed in at least one epidemiological study of high quality (i.e., the effect of biases on the study's findings was probably low and the precision of the effect estimate was adequate, e.g., the width of the 95% confidence interval as measured by the ratio of the upper to lower limit is ≤ 3) but there were inconsistencies in the results across studies and there was substantial doubt that the body of evidence is strong enough to rule out the effect of biases. This definition of limited/suggestive evidence is similar to that used by the Institute of Medicine (IOM, now renamed the Health And Medicine Division of the National Academies of Sciences, Engineering, and Medicine) (IOM 2008). The list of diseases included cancers of the kidney, liver, cervix, bladder, lung, breast, pancreas, esophagus, non-Hodgkin lymphoma, Hodgkin disease, leukemias, multiple myeloma, and several non-cancers including scleroderma, Parkinson disease, liver disease, kidney disease, generalized skin disorder, lupus, and spontaneous abortion.

After review of the assessments of TCE and PCE by EPA (EPA 2011, 2012; Chiu et al. 2013; Guyton et al. 2014), IARC (IARC 106, 2014) and NTP (NTP 2015), ATSDR added cancers of the brain and prostate and cardiac congenital malformations to its list of diseases with some association with either TCE or PCE exposure. Finally, the list was expanded to include rectal cancer and kidney diseases based on the findings from the Camp Lejeune mortality studies and studies of PCE-contaminated drinking water at Cape Cod MA (Paulu et al. 1999). For this assessment, ATSDR decided to focus on sixteen of these diseases: cancers of the kidney, hematopoietic system (leukemias, non-Hodgkin lymphoma, and multiple myeloma), liver, pancreas, prostate, breast, bladder, esophagus, rectum and brain, and Parkinson disease, kidney disease, scleroderma and cardiac congenital malformations. In future assessments, ATSDR will evaluate the remaining list of diseases as well as add new diseases to the list if future research indicates an association with TCE or PCE exposure.

Literature search

Reviews of epidemiological studies involving TCE and PCE exposure have been conducted by EPA (2011), IARC (2014) and NTP (2015). In addition, meta-analyses have recently been conducted by NCI researchers (Karami et al. 2012, Karami et al. 2013), EPA (EPA 2011, summarized in Scott and Jinot 2011), and an IARC workgroup (Vlaanderen et al. 2014) for TCE and kidney cancer, hematopoietic cancers and liver cancer, and PCE and bladder cancer. ATSDR utilized these reviews and meta-analyses to identify epidemiological studies for TCE and PCE. Meta-analyses of benzene and hematopoietic cancers (Khalade et al. 2010, Vlaanderen et al. 2011, 2012) were used to identify epidemiological studies for benzene. For vinyl chloride, we reviewed the IARC monograph 100F (2012) that evaluated vinyl chloride to identify epidemiological studies involving vinyl chloride exposure.

In addition, literature searches using PubMed were conducted to identify epidemiological studies conducted after each of the meta-analyses and reviews were completed. The keywords used in the search were the combination of each of the contaminants and each of the diseases being assessed. An additional search was conducted using the keyword "chlorinated solvents" in combination with each of the diseases being assessed. The PubMed search identified epidemiological studies published through September 4, 2015. Subsequently a PubMed search was conducted to identify epidemiological studies published through August 12, 2016. All meta-analyses that evaluated epidemiological studies were identified either from the reports by IARC, EPA and NTP or by the literature search and are included in this assessment. All epidemiological studies that were published after these reports and meta-analyses

were conducted were identified by the literature search and included in this assessment. Epidemiological studies that evaluated exposure-response relationships, whether included in a meta-analysis or not, were included in this assessment. Also identified by the literature search and considered in this assessment were published articles that reviewed the epidemiological evidence for the chemicals and diseases assessed in this document.

A literature search was not conducted for animal studies. Instead, information from animal studies, and information on possible disease mechanisms, were obtained from a review of the EPA, IARC and NTP reports and published articles that reviewed the epidemiological evidence. Information on animal studies and mechanism were also obtained from the epidemiological studies identified via the literature search or that were included in the meta-analyses.

Classification of Evidence

Several classification systems have been develop to reflect the strength of the evidence for a causal relationship between an exposure and a particular health effect (IOM 2012). The IARC, EPA and NTP have established classification systems for exposures that may pose a cancer hazard. The Institute of Medicine has adopted classification systems to evaluate non-cancer endpoints as well as cancers. These classification systems were developed under different mandates and therefore differ in their approach to the evidence (IOM 2012). For example, the IARC system separately evaluates and rates the human, animal, and mechanistic/other data before integrating these three types of evidence into one overall classification. On the other hand, the IOM reports on Agent Orange did not separately evaluate and then integrate these three types of evidence into one overall classification. Instead, IOM based the assessment of evidence on the epidemiological studies and used toxicological and mechanistic information to assess biological plausibility (IOM 2008). Although classification schemes and methods differ across these agencies, these differences do not necessarily result in different conclusions concerning the evidence for causality.

Because the focus of ATSDR's assessment was primarily on the epidemiological evidence, and non-cancers as well as cancers were assessed, the approach used by the IOM to assess evidence for causation was most appropriate. However, the IOM used a different classification scheme for its Agent Orange reports than for its Gulf War reports (IOM 2008). Moreover, the Gulf War classification scheme has changed the definition of its categories (while retaining the names of the categories) over time.

The classification scheme adopted for this report is the one recommended by an IOM panel that reviewed the VA's presumptive disability decision-making process for veterans (IOM 2008). This scheme makes clear when the evidence for causality is "at least as likely as not" or at the level of "equipoise and above." ATSDR adopted this scheme because of its focus on the epidemiological evidence for causation (i.e., there is no category for evidence of a statistical association). Additionally, the scheme is one that is already in use by the U.S. Department of Veterans Affairs (VA) in its decision-making concerning compensation for service-related disability compensation claims. The issue of compensation has been of major concern for the Camp Lejeune community. The classification scheme uses four categories:

1. Sufficient: The evidence is sufficient to conclude that a causal relationship exists.

2. Equipoise and Above[1]: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists.

3. Below Equipoise: The evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically informed judgment.

4. Against: The evidence suggests the lack of a causal relationship.

The IOM panel anticipated that if the evidence for causation was categorized as "sufficient" or as "equipoise and above," then the VA would consider a presumptive service connection based on the causal evidence. If the evidence for causation was categorized as "below equipoise," then the VA might reconsider the evidence at a later date as more research becomes available. This approach would be in agreement with VA policy to give the benefit of the doubt to the veteran (IOM 2008).

Classification scheme categories

Sufficient evidence for causation: the evidence is sufficient to conclude that a causal relationship exists. This category would be met, for example, if:

1. There is sufficient evidence from human studies in which chance and biases (including confounding) can be ruled out with reasonable confidence, **or**

2. There is less than sufficient evidence from human studies but sufficient evidence in animal studies and strong evidence that the agent acts through a relevant mechanism in humans.

Sufficient evidence from human studies can be provided by a meta-analysis and/or by several studies considered to have high utility.

Considerations in assessing the evidence include several of Hill's viewpoints: (1) temporal relationship, (2) consistent positive associations (e.g., risk ratio or odds ratio greater than 1.1), (3) magnitude of the effect estimate (e.g., risk ratio, odds ratio), (4) exposure-response relationship, and (5) biological plausibility (Hill 1965).

Equipoise and above evidence for causation: The evidence is sufficient to conclude that a causal relationship is at least as likely as not, but not sufficient to conclude that a causal relationship exists. This category would be met, for example, if:

1. The degree of evidence from human studies is less than sufficient but there is supplementary evidence from animal studies and/or mechanistic studies that supports causality, **or**

[1] In an earlier draft of this document, the category "Modest evidence for causation" was created and used to characterize evidence that was above equipoise but less than sufficient to conclude that a causal relationship existed.

2. A meta-analysis does not provide convincing evidence (e.g., the summary risk estimate is close to the null value of 1.0, i.e., ≤1.1), or if the meta-analysis observes a non-monotonic exposure-response relationship) but there is at least one epidemiological study considered to be of high utility occurring after the meta-analysis has been conducted, in which an association between the exposure and increased risk of the disease of interest has been found and in which chance and biases can be ruled out with reasonable confidence.

3. A meta-analysis has not been conducted, but there is at least one epidemiological study considered to be of high utility in which an association between the exposure and increased risk of the disease of interest has been found and in which chance and biases can be ruled out with reasonable confidence.

Below Equipoise evidence for causation: The evidence is not sufficient to conclude that a causal relationship is at least as likely as not, or is not sufficient to make a scientifically informed judgment. This is a rather broad category that encompasses:

- evidence sufficient to conclude an association exists but where there is some doubt that biases can be ruled out and the animal and mechanistic evidence is weak, or
- evidence for an association that is so limited that there is substantial doubt that biases can be ruled out, or
- insufficient evidence to determine whether an association exists.

Evidence against a causal relationship: The evidence suggests the lack of a causal relationship.

ATSDR's Methods Used to Assess the Strength of the Evidence for Causation

Comprehensive assessments of the evidence for causation for TCE, PCE, vinyl chloride and benzene have been conducted by IARC (IARC 97, 2008; 100F, 2012; 106, 2014), EPA (EPA 2011, 2012), and NTP (NTP 2015). ATSDR placed high weight on these assessments in reaching its conclusions concerning the evidence of causation for these chemicals and the diseases evaluated in these reports. ATSDR also placed high weight on the results of recent meta-analyses that were conducted by EPA (Scott and Jinot 2011) and other researchers (e.g., Karami et al. 2012, 2013; Vlaanderen et al. 2011, 2012, 2014). Meta-analyses were valuable for evaluating occupational studies. Many of these studies lacked precision in their effect estimates, in particular, when exposure-response trends were evaluated, due to small numbers of exposed with the disease of interest. Moreover, some of the meta-analyses were able to reduce the inconsistencies in findings across studies by taking into account study differences in exposure levels and in the quality of exposure assessments. Some of the meta-analyses also evaluated whether confounding bias, publication bias and between-study heterogeneity was a concern. Also given high weight were studies considered to be of high or moderate utility by NTP in its evaluation of TCE and kidney cancer, non-Hodgkin lymphoma and liver cancer (NTP 2015). These studies are identified in the tables for these diseases.

Epidemiological studies that were published after a meta-analysis was completed were included in the tables and evaluated in the assessment. Also assessed and included in the tables were all studies that evaluated exposure-response trends even if they were included in a meta-analysis. For these studies, the assessment focused on the results of the exposure-response analyses. Although not included in the tables, the assessment also considered information from animal studies and mechanistic information that was reported in the EPA, IARC and NTP reports, epidemiological studies, and epidemiological review articles.

In its assessment of each contaminant and disease, ATSDR highlighted epidemiological findings (i.e., effect estimates such as risk ratios, odds ratios, standardized mortality ratios and standardized incidence ratios) that:

1. Represented the risks to those most likely to have been exposed (and possibly less affected by exposure misclassification bias), such as effect estimates in the higher cumulative exposure or exposure intensity categories, higher probability of exposure categories, and higher duration of exposure categories, based on semi-quantitative or quantitative exposure assessments;

2. Minimally affected by healthy worker effect biases; and

3. Minimally affected by confounding bias due to smoking or other risk factors.

Also highlighted were findings from the evaluation of disease subgroupings (e.g., leukemia types) and findings from the evaluation of effect modification (e.g., analysis of possible susceptible populations such as those with a genetic polymorphism affecting a key metabolic pathway for the chemical under evaluation). For cancers with a high probability of survival, findings based on incidence data were highlighted because mortality data has several limitations including: (1) cancers may be missed if the exposure causes a less fatal form of the disease or if the cancer is not an underlying or contributing cause of death; and (2) cancer information provided by cancer registries (e.g., histological information and identification of primary and metastatic sites) has greater accuracy compared to the information available from the death certificate, therefore disease misclassification should be reduced for findings based on incidence data.

In the disease-specific tables, 95% confidence intervals were provided in order solely to indicate the level of precision or uncertainty in the effect estimates. An effect estimate (e.g., risk ratio, odds ratio, or standardized mortality ratio) was considered to have good precision (or less uncertainty) if the ratio of the upper limit to lower limit of its 95% confidence interval was ≤ 2.

In our assessment, we did not use confidence intervals to determine whether a finding was "statistically significant" nor did we use significance testing to assess the evidence for causality (Rothman et al. 2008). There are several limitations to the use of statistical significance testing (Rothman et al. 2008, Goodman 2008, Stang et al 2010). Moreover, a finding that does not achieve statistical significance nonetheless can provide important evidence for a causal association, while a finding that achieves statistical significance can often lack scientific and public health significance. Because of the limitations of statistical significance testing, it was not used to assess the epidemiological evidence. Instead, ATSDR assessment of the epidemiological evidence considered some of the viewpoints associated with

Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if ≤1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding.

1. Impact of Bias

Biases impact the validity of a study. Therefore, a consideration in the assessment of the evidence for causation was the impact of key biases on the findings of the studies. The key limitation of all the studies was **exposure misclassification**. The impact of exposure misclassification bias would likely be to bias dichotomous comparisons (e.g., exposed vs unexposed) towards the null if an effect of the exposure is truly present, and to distort exposure-response trends (e.g., the curve may flatten or attenuate at high exposure levels). It is possible for exposure misclassification bias to be "differential" (i.e., the bias is associated both with exposure and disease status). If differential, dichotomous comparisons can be biased toward or away from the null. For example, if exposures are assessed retrospectively (e.g., when cases and controls are interviewed about their past exposures), it is possible for exposure misclassification bias to be differential. However, differential exposure misclassification is not likely for studies that assess exposures via job-exposure matrices (JEMs), plant record reviews, exposure biomonitoring, or that historically reconstruct exposures via modeling.

The vast majority of the epidemiological studies that evaluated the health effects of TCE, PCE or vinyl chloride were occupational studies. Some of the occupational studies used semi-quantitative JEMs specific to a plant or industry to assess exposures. The JEMs were developed based on plant records, literature data, expert judgment from industrial hygienists, and/or exposure measurements (e.g., biomonitoring or work area sampling). Some studies used generic JEMs that linked a wide range of occupations and industries to exposure metrics for exposures of interest. All JEMs may introduce exposure misclassification bias because they assume that workers with the same job during a specific time period will have similar exposures. However, generic JEMs are likely to result in much greater exposure misclassification bias than industry-specific or plant-specific JEMs. Occupational studies that did not use JEMs based their exposure assessments on reviews of work history information (e.g. obtained via interview or from plant records) by experts in industrial hygiene. The quality of expert-assessed exposure levels depends on the amount and accuracy of the available information for the jobs being assessed. A few studies based their assessment of TCE exposure on urine trichloroacetic acid (TCA) measurements. However, urine TCA is not specific to TCE exposure and measures recent exposures that may not reflect exposures occurring in the past. Drinking water studies included in this review based their exposure assessments on modeled historical estimates of contaminant levels in the drinking water serving residences or workplaces. Information on the amount of water consumed by individuals was either limited (due to likely inaccuracies in the recall of past consumption habits) or unavailable.

Another important bias is due to the **Healthy worker/veteran effect**. This bias likely occurred in studies that compared incidence or mortality rates in worker or veteran cohorts with rates in the general population (Checkoway et al. 2004, McLaughlin et al. 2008, Kirkeleit et al. 2013). Such a bias would tend to produce underestimates of the effect of exposure, and in many situations, reduce measures of association (e.g., SIR or SMR) below the null value. Other selection biases such as loss to follow-up in

cohort studies or bias in the selection of cases or controls in case-control studies were generally minimal for most of the studies evaluated in this assessment.

2. Confounding assessment

Another issue for most of the studies is possible **confounding** due to co-exposures to other workplace or environmental chemicals. For example, dry cleaning workers employed before the early 1960s were likely exposed to other solvents besides PCE. Dry cleaning workers also used solvents for spot removal although these exposures would be considerably lower than exposures to the primary solvent. Workers in aircraft manufacturing or maintenance may have been exposed to TCE, PCE and other solvents. In the Camp Lejeune studies (Bove et al. 2014a, b) and the NJ drinking water studies (Cohn et al. 1994, Bove et al. 1995), both TCE and PCE appeared together as drinking water contaminants. However, the possibility of confounding occurs only if the co-exposure independently increases the risk of the disease under evaluation in addition to being correlated with the exposure of interest.

An additional concern was the possibility of confounding by non-occupational and non-environmental risk factors for the diseases under evaluation, such as smoking and alcohol consumption. However, for appreciable confounding (e.g., a change in the effect estimate by >20%) by smoking or any other risk factor to occur, at least two requirements must be met: (1) the risk factor must have an association with the outcome of interest at least as strong as the exposure of interest, and (2) the risk factor must also have a strong association with the exposure of interest. For the latter requirement to be met, the prevalence of the risk factor must be very different in the compared groups. This might occur for example when a worker (or veteran) cohort is compared to the general population. However, the prevalence of risk factors (other than the exposure of interest) should be similar when comparisons are made either internal to a cohort or between similar cohorts (e.g., similar workforces or similar military personnel), and therefore confounding would be expected to be minimal for these comparisons.

In general, substantial confounding due to smoking or any other risk factor is rare in occupational and environmental epidemiology. Even for studies of an occupational or environmental exposure and lung cancer, a summary measure (e.g., RR, OR) adjusted for smoking rarely differs by more than 20% from the unadjusted summary measure (Blair et al. 2007). In any case, the amount of bias due to confounding will not be greater than the weaker of these two associations: (1) between the exposure of interest and the confounder; (2) between the confounder and the disease of interest (Smith and Kriebel 2010).

Many of the studies included in the meta-analyses or listed in the tables did have information on smoking and were able to adjust for smoking if confounding was present. Most of the studies that did not have information on smoking were able to indirectly assess whether confounding due to smoking affected the results by evaluating whether a smoking-related disease that was not known to be associated with the exposure of interest was elevated in the study. Another indirect approach to evaluate possible confounding due to smoking would be to evaluate all smoking-related diseases in the study for which the risk from smoking is known (or expected to be) much larger than the risk from the exposure of interest. If appreciable confounding due to smoking were present, one would expect that all these diseases would be elevated for the exposure of interest.

Many of the studies evaluated, or adjusted for, risk factors in addition to smoking such as alcohol consumption and socioeconomic status. The appendix lists the studies included in the tables, whether or not they evaluate smoking as a possible confounder, and any additional potential confounders.

Assumptions on Duration of Exposure

One objective of this report was to evaluate whether there was sufficient information in the scientific literature to determine a minimum duration at Camp Lejeune, or a minimum level of exposure, necessary to increase the risk of one or more of the diseases being assessed. The 2012 Honoring America's Veterans and Caring for Camp Lejeune Families Act established a minimum duration at Camp Lejeune of 30 days in order to be eligible for health benefits under the Act. It is unclear how the minimum duration was established for this legislation. However, the evidence from the epidemiological studies included in this assessment is not sufficient to contradict this minimum duration. Moreover the results from the Camp Lejeune mortality studies suggest that a 30 day minimum duration requirement may be appropriate since elevated risks for some of the diseases evaluated were observed for exposure durations of 1-3 months. These results should not be surprising given that the levels of TCE, PCE and vinyl chloride measured or estimated in the drinking water systems at Camp Lejeune considerably exceeded their respective MCLs.

The studies evaluated in this report provide very limited information concerning the level or duration of exposure associated with an increased risk of a cancer or other disease. For example, those studies that evaluated cumulative exposure or exposure duration often used wide categorizations (e.g., duration of exposure > 0 to 5 years). An additional interpretative difficulty is the possible inverse relationship between duration and exposure intensity, e.g., high exposure intensities may require only a short duration of exposure whereas low exposure intensities may require longer exposure durations. Although cumulative exposure is a useful metric, it obscures this interplay between duration and intensity. Specifying a minimum duration of exposure also presupposes that there is a known threshold amount of exposure below which there is no excess risk. However, there is no compelling evidence that such thresholds exist for these contaminants and the cancers and other diseases evaluated in this report.

For cardiac birth defects, it is possible that very short durations of exposure to the mother may be sufficient if the exposure occurs during the relevant vulnerability period for cardiac defects, i.e., 3-9 months gestation. In-utero exposures have been associated with increased risk of childhood leukemia (Costas et al. 2002).

Given that sufficient evidence for a threshold is lacking, ATSDR recognizes that a decision to establish a specific minimum exposure duration for policy purposes will primarily be based on social, economic and legal factors.

Presentation of Findings

An overall summary table is provided that lists each disease and ATSDR's assessment of the evidence of causality for each chemical. In addition, a table for each disease was created followed by a narrative that includes the assessment of the evidence for each chemical and ATSDR's conclusions. Each disease-specific table first lists the results from meta-analyses that have been conducted. Next, the table lists the results from epidemiological studies that: (1) were not included in meta-analyses because they appeared after the meta-analyses were conducted; and/or (2) contained information on exposure-response trends (e.g., cumulative exposure, exposure duration, employment duration, exposure intensity, probability of exposure, or exposure biomarker); and/or (3) are included because no meta-analysis has been conducted to date. The studies in most of the tables are grouped in the following manner: cohort studies of TCE and PCE exposures at industrial facilities, case-control studies of occupational exposures to TCE and PCE, studies of dry cleaning workers, vinyl chloride worker studies, benzene worker studies, and drinking water studies including the studies conducted at Camp Lejeune. (For some diseases there are too few studies of each category to group in this manner. For these tables, cohort studies are grouped together, then case-control studies, and then the drinking water studies.) Following each table, a summary of the conclusions for that disease from the reviews by EPA, IARC and NTP, if available, are provided, followed by ATSDR's assessment.

ATSDR's assessment includes a brief discussion of the meta-analyses and key studies. Animal study information from the reviews by IARC, EPA and/or NTP are also provided. If available, mechanistic information from animal or human studies specific to the disease and chemical under evaluation are also presented. A summary statement of the evidence is then provided.

In an appendix, a table is provided listing each study and information concerning possible confounding by smoking as well as information on whether other key risk factors were assessed or adjusted for.

Overall Summary of the Evidence*

Disease	Chemicals	Meta-analysis Citations	ATSDR Conclusions
Kidney Cancer	TCE	Kelsh 2010; Scott (EPA) 2011; Karami (NCI) 2012	Sufficient evidence for causation
	PCE		Below equipoise evidence for causation
Non-Hodgkin Lymphoma	TCE	Kelsh 2010; Scott (EPA) 2011; Karami (NCI) 2013	Sufficient evidence for causation.
	PCE		Equipoise and above evidence for causation
	Benzene	Steinmaus 2008; Kane 2010; Vlaanderen 2011	Sufficient evidence for causation
Multiple Myeloma	TCE	Alexander 2006; Karami (NCI) 2013	Equipoise and above evidence for causation
	PCE		Below equipoise evidence for causation
	Benzene	Infante 2006; Vlaanderen 2011	Equipoise and above evidence for causation
Leukemias	TCE	Alexander 2006; Karami (NCI) 2013	Equipoise and above evidence for causation for all types of leukemia
	PCE		Below equipoise evidence for causation
	Benzene	Khalade 2010; Vlaanderen 2011; Vlaanderen 2012	Sufficient evidence for causation for all types of leukemia
	Vinyl chloride	Boffetta 2003	Below equipoise evidence for causation
Liver Cancer	TCE	Alexander 2007; Scott (EPA) 2011	Equipoise and above evidence for causation
	PCE		Below equipoise evidence for causation
	Vinyl chloride	Boffetta 2003	Sufficient evidence for causation
	Benzene		Below equipoise evidence for causation
Pancreatic Cancer	TCE	Ojajarvi 2001, 2007	Below equipoise evidence for causation
	PCE	Ojajarvi 2001, 2007	Below equipoise evidence for causation
	Benzene		Below equipoise evidence for causation
	Vinyl chloride	Ojajarvi 2001, 2007	Below equipoise evidence for causation
Prostate Cancer	TCE	Morgan 1998	Below equipoise evidence for causation
	PCE		Below equipoise evidence for causation
	Vinyl chloride		Below equipoise evidence for causation
Breast Cancer (male & female)	TCE		Below equipoise evidence for causation
	PCE		Below equipoise evidence for causation
	Benzene		Below equipoise evidence for causation

Disease	Chemicals	Meta-analysis Citations	ATSDR Conclusions
Bladder Cancer	TCE		Below equipoise evidence for causation
	PCE	Vlaanderen (IARC) 2014	Sufficient evidence for causation
	Vinyl chloride		Below equipoise evidence for causation
	Benzene		Below equipoise evidence for causation
Parkinson Disease	TCE		Equipoise and above evidence for causation
	PCE		Below equipoise evidence for causation
Kidney Diseases	TCE		Equipoise and above evidence for causation for end-stage renal disease
	PCE		Equipoise and above evidence for causation for end-stage renal disease
Esophageal Cancer	TCE		Below equipoise evidence for causation
	PCE		Below equipoise evidence for causation
	Benzene		Below equipoise evidence for causation
Rectal Cancer	TCE		Below equipoise evidence for causation
	PCE		Below equipoise evidence for causation
Brain/CNS Cancers	TCE		Below equipoise evidence for causation
	PCE		Below equipoise evidence for causation
	Vinyl chloride	Boffetta 2003	Below equipoise evidence for causation
Systemic Sclerosis/ Scleroderma	TCE	Cooper 2009; Zhao 2016	Equipoise and above evidence for causation
	PCE	Zhao 2016	Below equipoise evidence for causation
	Benzene	Zhao 2016	Below equipoise evidence for causation
Cardiac Defects	TCE		Sufficient evidence for causation
	PCE		Below equipoise evidence for causation

* The evidence for a causal association between each exposure and disease is presented in more detail in the following tables and accompanying text.

Individual Tables

Kidney Cancer

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Kelsh 2010 **meta-analysis**	TCE	Not reported	sRR=1.42 (1.13, 1.77) – 23 studies; "More likely exposed": sRR=1.34 (1.07, 1.67) – 8 cohort studies	"Shortest" duration: RR=1.50 (0.96, 2.36) – 7 studies "Longest" duration: RR=1.24 (0.69, 2.23) – 7 studies	"Low" cumulative exposure: RR=1.29 (0.68, 2.47) – 3 studies "High" cumulative exposure: RR=1.39 (0.75, 2.59) – 3 studies
Scott 2011, EPA **meta-analysis**	TCE	Not reported	sRR=1.27 (1.13, 1.43) – 15 studies; (11 incidence (I), 4 mortality M))		High cumulative exposure, summary RR=1.64 (1.31, 2.04) – 10 studies
Karami 2012 **meta-analysis**	TCE	478 (?)**	sRR=1.32 (1.17, 1.50) – 18 studies (9 cohort – 4 I, 5 M; 9 case-control – 8 I, 1 M)		—
Cohort Studies:					
Anttila 1995+ [9] Incidence 849 1967-1992	PCE (blood PCE)	2	SIR=1.82 (0.22, 6.56)		
Raaschou-Nielsen 2003 [1] Incidence 40,049 1964-1997	TCE (job title, plant air monitoring & Urine TCA data)	76		Duration of employment (yr) (SIR) # cases Men Women <1: 0.8 (0.5, 1.4) 14 1.1 (0.1, 3.8) 2 1-4.9: 1.2 (0.8, 1.7) 25 1.2 (0.2, 3.4) 3 ≥5: 1.6 (1.1, 2.3) 29 1.5 (0.3, 4.3) 3	
Zhao 2005¶ Incidence 5,049 1988-2000 **NTP: High Utility**	Aerospace TCE (JEM)	6 4			Cumulative Exposure (RR) Med: 1.9 (0.6, 5.2) High: 4.9 (1.2, 19.6)
Radican 2008+ Mortality 10,730 men¥ 1953-2000 **NTP: Moderate Utility**	Aircraft maintenance TCE (walk-through surveys, interviews, job tasks, air monitoring data)	16		Cumulative Exposure (unit-yr) HR 0-5: 1.9 (0.6, 6.0) – 10 cases 5-25: 0.3 (0.0, 2.8) – 1 case >25: 1.2 (0.3, 4.3) – 5 cases	Exposure intensity (HR) # cases Low, intermittent: 1.6 (0.5, 4.8) 15 Low, continuous: 1.8 (0.6, 5.6) 11 Peak, infrequent: 1.0 (0.2, 5.7) 2 Peak, frequent: 1.1 (0.3, 4.0) 6

Reference, type of cancer data, total # of subjects, follow-up period	Exposure^ (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Lipworth 2011[***] Mortality 5,830 (PCE) 1960-2008	Aircraft Manufacturing PCE (JEM)	13	Any exposure: SMR=0.80 (0.43, 1.37)	Duration of exposure (yr) (RR) # cases TCE <1: 0.84 (0.48, 1.47) 18 1-4: 1.10 (0.59, 2.04) 14 ≥5: 1.02 (0.55, 1.90) 15	PCE 1.26 (0.65, 2.45) 11 1.00 (0.50, 2.00) 10 1.02 (0.53, 1.99) 12
Hansen 2013 Incidence 5,553 Finland:1967-2004 Sweden: 1958-2003 Denmark: 1968-2008 **NTP: Moderate Utility**	TCE (urine TCA)	32 19	SIR=1.01 (0.70, 1.42) 20 yr lag: SIR=1.11 (0.67, 1.73)		Urine TCA (mg/L): (RR) <5: referent 5-25: 1.1 (0.5, 2.7) – 11 cases 25-50: 0.8 (0.2, 3.0) - 3 cases >50: 2.0 (0.8, 5.2) – 9 cases
Silver 2014 Mortality 34,494 1969-2009	Microelectronics firm TCE (JEM) PCE (JEM)	56			Cumulative exposure (5 exposure-yr) HR=1.24 (0.87, 1.77) HR=0.15 (0.01, 4.04)
Buhagen 2016 Incidence 997 males 1960-2010	Train maintenance TCE (union employment list)	13	SIR=1.7 (1.0, 3.0)		
Case-Control Studies:					
Pesch 2000[+] Incidence 935 cases 4,298 controls	Questionnaire and JTEM TCE PCE	M F 68 11 59 7 22 5 44 8 39 6 15 3		Cumulative exposure (percentiles) Odds ratios Males: 30th: 1.3 (1.0, 1.8) 60th: 1.1 (0.8, 1.5) 90th: 1.3 (0.8, 2.1) 30th: 1.2 (0.9, 1.7) 60th: 1.1 (0.7, 1.5) 90th: 1.3 (0.7, 2.3)	Females 1.3 (0.7, 2.6) 0.8 (0.4, 1.9) 1.8 (0.6, 5.0) 2.2 (0.9, 5.2) 1.5 (0.6, 3.8) 2.0 (0.5, 7.8)
Charbotel 2006[+] Incidence 86 cases 316 controls **NTP: High Utility**	TCE (occupational questionnaire & JTEM)	37	Ever exposed, OR=1.64 (0.95, 2.84)		Cumulative dose: (ORs) Low: 1.6 (0.8, 3.5) – 12 cases Med: 1.2 (0.5, 2.8) – 9 cases High: 2.2 (1.0, 4.6) - 16 cases

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Moore 2010[++] Incidence 1,097 cases 1,476 controls **NTP: High Utility**	TCE (occupational questionnaire & JTEM)	29	High confidence, any exposure: OR=2.05 (1.13, 3.73)	<1,080 hours, OR=1.22 (0.48, 3.12) – 9 cases; ≥1,080 hours, OR=2.86 (1.31, 6.23) – 20 cases	<1.6 ppm-years: OR=1.77 (0.64, 4.80) – 9 cases; ≥1.6 ppm-years: OR=2.23 (1.07, 4.64) – 20 cases <0.076 ppm intensity: OR=1.73 (0.75, 4.02) – 13 cases; ≥0.076 ppm intensity: OR=2.41 (1.05, 5.56) – 16 cases
Vlaanderen 2013 Incidence 76,130 cases 380,650 controls 1961-2005	 TCE (JEM) PCE (JEM) Benzene (JEM)	 1,217 1,556 1,372 375 333 314 1359 1435 1560	Tertiles of cumulative exposure: 1. HR=1.01 (0.95, 1.07) 2. HR=1.02 (0.97, 1.08) 3. HR=1.00 (0.95, 1.07) 1. HR=1.11 (0.99, 1.24) 2. HR=0.96 (0.86, 1.08) 3. HR=0.94 (0.83, 1.06) 1. HR=1.00 (0.94, 1.06) 2. HR=1.00 (0.95, 1.06) 3. HR=1.06 (1.00, 1.12)		>90th percentile cumulative exposure: (HRs) TCE: 0.86 (0.75, 0.98) 251 cases PCE: 0.81 (0.65, 1.01) 88 cases >90th percentile, intensity x freq. exp. TCE: 1.00 (0.90, 1.30) 387 cases PCE: 1.01 (0.82, 1.25) 103 cases
Christensen 2013[#] Incidence 177 cases 533 controls	TCE PCE	5 2 2 2	Any exposure: OR=1.0 (0.3, 2.9) "substantial": OR=0.7 (0.1, 3.2) Any exposure: OR=1.6 (0.3, 9.4) "substantial": OR=3.1 (0.4, 24)	–	–
Dry Cleaning Workers Studies					
Blair 2003 Mortality 5,369 1948-1993	Dry Cleaning	8	SMR=1.0 (0.4, 2.0)		Exposure intensity # cases Little/no: SMR=0.3 (0.0, 1.6) 1 Med/high: SMR=1.5 (0.6, 3.1) 7
Lynge 2006 Incidence 158 cases 785 controls 1970-2001	Dry Cleaning	29	RR=0.67 (0.43, 1.05)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Calvert 2011 Mortality 1,704 618 PCE-only 1,086 PCE-plus 1940-2004	Dry Cleaning (industry surveys, personal monitoring data, work history)	5 2 3	SMR=1.14 (0.37, 2.67) All SMR=1.35 (0.16, 4.89) PCE only SMR=1.04 (0.21, 3.04) PCE plus		
Selden 2011 Incidence 9,440 1985-2006	Dry Cleaning and Laundry Workers: (plant survey, work history)	 29 10 19	Any exposure All: SIR=1.04 (0.69, 1.49) Men: SIR=1.06 (0.51, 1.94) Women: SIR=1.03 (0.62, 1.60)		
Drinking water studies:					
Aschengrau 1993 Incidence 35 cases 777 controls	PCE-contaminated drinking water (modeled)	6	Ever exposed: RR=1.23 (0.40, 3.11)		
Bove 2014a (Camp Lejeune Marines/Navy) Mortality 154,932: Camp Lejeune 154,969: Camp Pendleton 1979-2008	VOC contaminated drinking water (modeled) vs U.S. population vs. Camp Pendleton	42	 SMR=1.16 (0.84, 1.57) HR=1.35 (0.84, 2.16)	Exposure duration (months) 1-3: OR=1.3 (0.4, 4.5) 3 cases 4-6: OR=1.2 (0.3, 5.5) 2 cases 7-12: OR=1.9 (0.7, 5.2) 6 cases >12: OR=1.7 (0.8, 3.6) 20 cases	Cumulative Exposure (HR) # cases TCE Low: 1.5 (0.6, 3.6) 11 Med: 1.2 (0.5, 3.1) 8 High: 1.5 (0.6, 3.6) 11
Bove 2014b (Camp Lejeune Civilian workers) Mortality 4,647: Camp Lejeune 4,690: Camp Pendleton 1979-2008	VOC contaminated drinking water U.S. population vs. Camp Pendleton	7	 SMR=1.30 (0.52, 2.67) HR=1.92 (0.58, 6.34)	5 of 7 deaths had any residential exposure duration >12 months	All 7 deaths had residential cumulative exposures above the median for PCE, TCE and VC

* Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.

** One included study did not report the number of exposed cases. The rest of the included studies reported a total of 478 exposed cases.

° Included in the table for information on PCE.

¶ Included in the EPA meta-analysis

+ Included in the EPA, Karami et al. 2012, and Kelsh et al. 2010 meta-analyses

++ Included in the EPA and Karami et al. 2012 meta-analyses

[+++] Included in the Karami et al. 2012 meta-analysis. Note: only the PCE findings for Lipworth et al. 2011 are included in the table because no meta-analyses have been conducted for PCE and kidney cancer. There was no exposure-response information for PCE or TCE in the Lipworth et al. study.

[#] Exposure assessment based on interviews and expert assessment

[¥] There were only 2 deaths due to kidney cancer among the 3,725 women workers.

RR: Risk Ratio

OR: Odds Ratio

SMR: Standardized Mortality Ratio

SIR: Standardized Incidence Ratio

95% CI: 95% Confidence Interval

sRR: Summary Risk Ratio

HR: Hazard Ratio

JEM: Job-exposure matrix

JTEM: job-task exposure matrix

Urine-TCA: Urine levels of the TCE metabolite, trichloroacetic acid

I: Incidence; M: mortality

VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)

Note: cases listed in the table are exposed cases unless otherwise defined.

Summary of EPA, IARC and NTP reviews of TCE and kidney cancer

EPA Toxicological Review of TCE (EPA 2011, p. 4-632): "...TCE is characterized as carcinogenic to humans by all routes of exposure. This conclusion is based on convincing evidence of a causal association between TCE exposure in humans and kidney cancer. The kidney cancer association cannot be reasonably attributed to chance, bias, or confounding."

IARC (IARC 2014, p. 189): "There is *sufficient evidence* in humans for the carcinogenicity of trichloroethylene. Trichloroethylene causes cancer of the kidney.

NTP Monograph on TCE (NTP 2015, p. 177-178): "Epidemiological studies have demonstrated a causal relationship between trichloroethylene exposure and kidney cancer based on consistent evidence of increased risk across studies with different study designs, in different geographical areas, and in different occupational settings; evidence of increasing cancer risk with increasing level or duration of exposure; and statistically significant increased risks of kidney cancer across studies combined in two meta-analyses. Overall, increased risks of kidney cancer were found among individuals with the highest exposure in the most informative studies (i.e., studies with higher levels of exposure to trichloroethylene and better assessments of exposure and disease...." "... biases or confounding by known or suspected occupational co-exposures, smoking, or other lifestyle factors are unlikely to explain the positive findings across studies..." "Toxicokinetic and mechanistic data in both humans and animals provide credible evidence for the biological plausibility of the proposed mechanisms of trichloroethylene's carcinogenicity in humans."

ATSDR Assessment

In the assessment of the evidence for causation, ATSDR placed high weight on assessments conducted by EPA, NTP and IARC as well as meta-analyses. High weight was also given to a study that was considered of moderate or high utility by the NTP, evaluated a susceptible subpopulation, or provided mechanistic information. Our assessment of the epidemiological evidence considered some of the viewpoints associated with Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if ≤ 1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding.

TCE

The three meta-analyses that have been conducted consistently observed an elevated summary RR in the 1.3-1.4 range, and higher cumulative exposures were observed to increase the risk of kidney cancer. The EPA (Scott and Jinot 2011) and Karami et al. 2012 meta-analyses reported that there was no between-study heterogeneity or evidence of publication bias. The EPA meta-analysis (Scott and Jinot 2011) concluded

that confounding by smoking and other risk factors would have a minimal impact on the meta-analysis results. NTP (2015) in its assessment stated that the increased risks found across the epidemiological studies were unlikely to be explained by biases. IARC (2014) and EPA (2011) have determined that there is sufficient evidence in humans that TCE causes kidney cancer. NTP (2015) noted that increased risks were observed in studies with higher levels of exposure and better exposure assessments. The NTP concluded: "Epidemiological studies have demonstrated a causal relationship between trichloroethylene exposure and kidney cancer based on consistent evidence of increased risk across studies with different study designs, in different geographical areas, and in different settings; evidence of increasing cancer risk with increasing level or duration of exposure; and meta-analyses showing statistically significantly increased cancer risk across studies."

Since the meta-analyses were conducted, two Camp Lejeune studies and five other recent studies have been published. Of these recent studies, Hansen et al. 2013 had the best study design with: (1) a large pooled cohort, (2) evaluation of cancer incidence, (3) documented exposure based on TCE metabolite biomonitoring, (4) minimal confounding by smoking especially for the internal (urinary TCA) analysis, and (5) an analysis of exposure-response trend. This study observed an elevated risk among those with the highest levels of urine TCA (RR=2.0; 95% CI: 0.8, 5.2). However, this study was limited by the low exposures among most of its workers, the reliance on a few urine TCA measurements to assess exposures and the small numbers of exposed cases in the exposure-response analysis. Two recent studies that did not observe an increased risk for kidney cancer, Vlaanderen et al. 2013 and Christensen et al. 2013, had severe limitations. The Vlaanderen et al. study used a generic JEM that the authors admitted was likely to introduce considerable exposure misclassification. Moreover, only a small percentage of the study population received high exposures to either TCE or PCE. The Christensen et al. study had very few exposed cases. Two other recent studies, Silver et al. 2014 and Buhagen et al. 2016, and the two Camp Lejeune studies (Bove et al. 2014 a,b) observed increased risks of kidney cancer.

One study included in both the NCI and EPA meta-analyses, Moore et al. 2010, was of particular importance since it not only evaluated exposure-response trends but also the interaction between TCE exposure and genotypes for the GSTT1 and renal-CCBL1enzymes. These enzymes are highly active in the kidney and involved in the bioactivation of TCE (via GSH-conjugation pathway). This study was considered of "high utility" by the NTP (2015) review of TCE and ATSDR concurs. In addition to observing exposure-response trends for TCE exposure and kidney cancer, the study also found that those exposed to TCE with at least one intact GSTT1 allele had elevated risks for kidney cancer, but those with a functionally inactive GSTT1 enzyme (i.e., with two deleted alleles, the null genotype) had **no elevated risk**. Findings for the interaction between TCE exposure and minor alleles for the renal-CCBL1 enzyme supported the findings for the GSTT1 enzyme. The findings of this study are in agreement with the hypothesized mechanism for TCE-induced kidney cancer and therefore provide strong evidence for causality.

Animal and mechanistic information: "The mode of action for trichloroethylene-induced kidney cancer is not completely understood but the available data provide support for a mutagenic and cytotoxic mode of action mediated by GSH-conjugation-derived metabolites. There is experimental evidence that GSH metabolites (particularly DCVC) are genotoxic and nephrotoxic and are both formed in and delivered to the kidney following exposure to trichloroethylene." (NTP Monograph on

Trichloroethylene, 2015, p. 106.) Exposure to TCE via inhalation or stomach tube has been observed to cause kidney cancer in rats (NTP 2015).

Exposure-Response: The Moore et al. 2010 study and the Raaschou-Nielsen 2003 study found increased risk with increasing duration of exposure. The Moore et al. 2010 study also suggested that an elevated risk could occur with a short duration of exposure (OR=1.2, 95% CI: 0.5, 3.1 for ≤6 month exposure duration). The Camp Lejeune mortality study of Marines/Navy personnel (Bove et al. 2014a) found an elevated risk among those with exposure ≤3 months to the drinking water contaminants including TCE (RR=1.3, 95% CI: 0.4, 4.5), although higher risks were observed with exposure durations >6 months. Both the Scott and Jinot 2011 and the Kelsh et al. 2010 meta-analyses found an increased risk with higher cumulative exposures. In the Camp Lejeune study of Marines and Navy personnel (Bove et al. 2014a), there was a monotonic trend for cumulative exposure when all the contaminant levels were summed, but not for TCE or the other contaminants when analyzed separately.

Conclusion: ATSDR concurs with the evaluations made by IARC, EPA and NTP. Based on the overall consistent findings of increased risks of kidney cancer from exposures to TCE and the supporting mechanistic information, there is **sufficient evidence for causation for TCE and kidney cancer**.

PCE

No meta-analyses have been conducted for PCE and kidney cancer. The epidemiological studies have not consistently observed an increased risk. Increased risks were found in the Camp Lejeune studies (Bove et al. 2014 a, b) and the Cape Cod drinking water study (Aschengrau et al. 1993) as well as the Pesch et al. 2000 and the Christensen et al. 2013 studies. No increased risks were observed in the Lipworth et al. 2011, Vlaanderen et al. 2013, and Silver et al. 2014 studies. A major limitation of several of the studies was the small number of exposed cases. In one bioassay, PCE exposure via inhalation resulted in an increase in the combined incidence of benign and malignant tubular-cell kidney tumors in male rats (Guyton et al. 2014).

Conclusion: ATSDR concludes that there is **below equipoise evidence for causation for PCE and kidney cancer** due to the lack of consistency in the findings from the epidemiological studies.

Non-Hodgkin Lymphoma (NHL)

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Mandel 2006 **Meta-analysis**	TCE (All workers) "more likely exposed"	429 137	sRR =1.29 (1.00, 1.66) 8 studies (4 I, 4 M) sRR =1.59 (1.21, 2.08) 7 studies (4 I, 3 M)	<5 yrs exp.: sRR=1.47 (1.08, 2.0) ≥5 yrs exp.: sRR=1.60 (1.20, 2.10)	low intensity: sRR=2.33 (1.29, 3.91) high intensity: sRR=2.11 (0.76, 5.84)
Scott 2011 **Meta-analysis (EPA)**	TCE	Not reported	Summary RRs/ORs: # studies: All: 1.23 (1.07, 1.42) 17 (13 incidence (I), 4 mortality (M)) Cohort: 1.33 (1.13, 1.58) 9 (5 I, 4 M) Case-control: 1.11 (0.89, 1.38) 8 (8 I)		higher TCE exposure, summary RRs/ORs: All studies: 1.43 (1.13, 1.82) Cohort: 1.60 (1.24, 2.08) Case-control: 1.29 (0.76, 2.20)
Karami 2013 **Meta-analysis**	TCE 532 (?) exposed cases** TCE exposure confirmed by urine TCA (21 exposed cases)	Summary RRs/ORs: # studies: All: 1.32 (1.14, 1.54) 19 Cohort: 1.52 (1.29, 1.79) 10 (6 I, 4 M) Case-control: 1.14 (0.93, 1.40) 9 (9 I) RR=2.15 (1.34, 3.45) 3 (3 I)		Cohort studies: "low": RR=1.30 (0.92, 1.84) "high": RR=1.56 (1.02, 2.40) Case-control studies: "low": OR=1.46 (0.78, 2.73) "high": OR=1.18 (0.60, 2.34)	Cohort studies: "low intensity": RR=1.68 (1.14, 2.46) "high intensity": RR=1.27 (0.83, 1.96) Case-control studies: "low intensity": RR=1.06 (0.79, 1.42) "high intensity": RR=1.42 (0.86, 2.33)
Steinmaus 2008 **Meta-analysis**	Benzene	228 (?)[δ] 133 23 133 23	sRR=1.22 (1.03, 1.46) 22 studies (6 cohort studies, 4 mortality and 2 incidence; 16 case-control studies) sRR=1.49 (1.15, 1.92) 13 high exposure studies sRR=2.12 (1.11, 4.02) 6 high exposure studies that did not use self-reported data sRR=1.53 (1.19, 1.96) 13 high exposure studies adjusted for healthy worker effect sRR=2.26 (1.29, 3.97) 6 high exposure studies that did not use self-reported data, adjusted for healthy worker effect		
Kane 2010 **Meta-analysis**	Benzene	Not reported	sRR=1.11 (0.94, 1.30) 24 studies (6 cohort, 16 case-control, 1 cancer registry study, 1 death certificate study)		
Vlaanderen 2011 **Meta-analysis**	Benzene	647 106 69 50	Quantitative & qualitative exposure assessment: mRR=1.00 (0.89, 1.13) 33 cohort studies[α] (6 incidence, 27 mortality) Quantitative to some industrial hygiene sampling: mRR=1.03 (0.70, 1.51) 8 cohort studies[α] (2 incidence, 6 mortality) Quantitative or semi-quantitative estimates: mRR=1.04 (0.63, 1.72) 7 cohort studies[α] (1 incidence, 6 mortality) Quantitative exposure assessment: mRR=1.27 (0.90, 1.79) 6 cohort studies (1 incidence, 5 mortality)		
Cohort Studies:					
Anttila 1995[¶] Incidence 3,089 TCE workers 849 PCE workers 1967-1992	PCE (blood PCE levels)	3	Any exposure: SIR=3.76 (0.77, 11.0)		TCE exposure: Urine TCA (μmol/L) # cases <100: SIR=2.01 (0.65, 4.69) 5 ≥100: SIR=1.40 (0.17, 5.04) 2

Reference, type of cancer data, total # of subjects, follow-up period	Exposure[a] (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Raaschou-Nielsen 2003 [g] Incidence 40,049 1964-1997	TCE (job title, plant air monitoring & Urine TCA data) TCE (20 year exposure lag)	96 83 13 31 7	Any exposure: Men: SIR=1.2 (1.0, 1.5) Women: SIR=1.4 (0.7, 2.3) Men: SIR=1.3 (0.9, 1.9) Women: SIR=1.9 (0.8, 3.9)	High exposure group: SIR=1.5 (1.2, 2.0) 65 Duration of employment (years): 1-4.9: SIR=1.5 (1.1, 2.1) 35 ≥5: SIR=1.6 (1.1, 2.2) 30	—
Radican 2008[c] Mortality 14,455 1953-2000 **NTP: Moderate Utility**	Aircraft maintenance TCE (JEM) PCE (JEM)	46 37 9 5 2	Any TCE exposure: HR=1.36 (0.77, 2.39) Men: HR=1.56 (0.72, 3.35) Women: HR=1.18 (0.49, 2.85) HR=2.32 (0.75, 7.15) males HR=2.35 (0.52, 10.7) females	Cumulative exposure score (unit-yr) Men (HR) # Women (HR) # 0-5: 1.8 (0.8, 4.2) 18 1.5 (0.5, 4.7) 4 5-25:1.2 (0.4, 3.2) 7 0 >25: 1.5 (0.6, 3.7) 12 1.3 (0.5, 3.8) 5	Men: HR # cases Low, intermittent: 1.5 (0.7, 3.3) 25 Low, continuous: 1.7 (0.8, 4.0) 20 Peak, infrequent: 1.9 (0.7, 5.2) 7 Peak, frequent: 1.6 (0.7, 3.7) 16 Women HR # cases Low, Intermittent: 1.4 (0.5, 4.0) 5 Low, Continuous: 1.0 (0.2, 4.7) 2 Peak, Infrequent: 3.5 (1.0, 12) 3 Peak, Frequent: 1.3 (0.5, 3.5) 6
Lipworth 2011[f] Mortality 5,443 (TCE) 5,830 (PCE) 1960-2008	Aircraft manufacturing TCE (JEM) PCE (JEM)	 50 36	Any exposure: SMR=1.31 (0.97, 1.73) SMR=1.43 (1.00, 1.98)	Years exposed (RR, # exposed cases): TCE PCE <1: 0.8 (0.5, 1.5) 18 1.3 (0.7, 2.5) 11 1-4: 1.1 (0.6, 2.0) 14 1.0 (0.5, 2.0) 10 >4: 1.0 (0.6, 1.9) 15 1.0 (0.5, 2.0) 12	—
Hansen 2013 Incidence 5,553 Finland:1967-2004 Sweden: 1958-2003 Denmark: 1968-2008 **NTP: Moderate Utility**	TCE (urine TCA)	32 6 38	Men: SIR= 1.55 (1.06, 2.20) Women: SIR=0.63 (0.23, 1.37) All: SIR=1.26 (0.89, 1.73)		Urine TCA (mg/L) 5-25: RR=1.16 (0.53, 3.09) 14 cases >25-50: RR=1.56 (0.63, 3.81) 8 cases >50: RR=0.66 (0.21, 2.03) 4 cases
Bahr 2011 Mortality 5,016 white males 1953-2003	TCE (Qualitative JEM)	23 12 11	Exposure Level 2: SRR=1.31 (0.47, 3.65) 3: SRR=0.75 (0.27, 2.12)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Silver 2014 Mortality 34,494 1969-2009	Microelectronics plant (JEM) TCE PCE	98	Cumulative exposure, 5 exposure-years: HR=0.87 (0.57, 1.35) HR=1.25 (0.90, 1.73)	—	—
Case-Control Studies:					
Miligi 2006® Incidence 1,135 cases: NHL and chronic lymphocytic leukemia CLL) 1,246 controls	TCE PCE Benzene			Medium/high exposure intensity Duration of exposure (OR): **TCE** ≤15 years: 1.1 (0.6, 2.1) 22 cases >15 years: 1.0 (0.5, 2.6) 12 cases **PCE** ≤15 years: 1.3 (0.5, 3.3) 10 cases >15 years: not estimated. 3 cases **Benzene** <15 years: 1.2 (0.7, 2.0) 39 cases >15 years: 2.9 (0.9, 9.0) 14 cases	Exposure intensity: OR # cases **TCE** Very low/low: 0.8 (0.5, 1.3) 35 Medium/high: 1.2 (0.7, 2.0) 35 **PCE** Very low/low: 0.6 (0.3, 1.2) 18 Medium/high: 1.2 (0.6, 2.5) 14 **Benzene** Very low/low: 0.6 (0.4, 0.9) 49 Medium/high: 1.6 (1.0, 2.4) 58

Seidler 2007¶
Incidence
589 cases of NHL
710 controls
	TCE
	
	PCE
	
	Benzene
			Cumulative exposure (percentiles):
			B-cell NHL (N=550) # cases
			>0-50%: OR=0.7 (0.5, 1.2) 32
			>50-90%: OR=0.8 (0.5, 1.3) 27
			>90%: OR=2.3 (1.0, 5.3) 17
			
			>0-50%: OR=0.9 (0.4, 2.0) 12
			>50-90%: OR=1.0 (0.5, 2.3) 12
			>90%: OR=3.2 (0.6, 16.7) 5
			
			>0-50%: OR=0.9 (0.6, 1.4) 41
			>50-90%: OR=1.0 (0.6, 1.5) 39
			>90%: OR=1.0 (0.4, 2.3) 11
				T-cell NHL (N=33) # cases
				OR=0.7 (0.2, 3.3) 2
				OR=1.1(0.2, 5.1) 2
				OR=4.7 (0.8, 26) 2
				
				(1 case in each exposure stratum)
				
				OR=1.2 (0.3, 4.4) 3
				OR=1.7 (0.5, 6.1) 3
				— (1 case)
					Cumulative exposure (percentiles)
					all NHL cases (B-cell & T-cell) # cases
					>0-50%: OR=0.7 (0.4, 1.1) 40
					>50-90%: OR=0.7 (0.5, 1.2) 32
					>90%: OR=2.3 (2.1, 4.8) 21
					
					>0-50%: OR=1.1 (0.5, 2.3) 16
					>50-90%: OR=1.0 (0.5, 2.2) 14
					>90%: OR=3.4 (0.7, 17) 6
					
					>0-50%: OR=0.9 (0.6, 1.3) 53
					>50-90%: OR=1.0 (0.7, 1.5) 47
					>90%: OR=0.8 (0.4, 1.9) 12

Christensen 2013 Incidence 215 cases 2,341 controls 1979-1985	TCE PCE	7 3 3 2	"any"exposure: OR=1.3 (0.5, 3.4) "substantial": OR= 0.9 (0.2, 3.4) "any"exposure: OR=2.2 (0.5, 10) "substantial": OR=2.6 (0.4, 19)	—	—

Reference, type of cancer data, total # of subjects, follow-up period	Exposure (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Cocco 2013 Incidence 3,788 cases of NHL 4,279 controls 1991-2004 **NTP: High Utility**	Probability of TCE exposure	335 109 176 50 90 28 51 11 59 13 37 9 70 23 36 11	Odds ratio (NHL, all types): Low: 1.0 (0.8, 1.3) Med: 0.9 (0.7, 1.1) High: 1.4 (0.9, 2.1) <u>Diffuse large B-cell lymphoma</u>: Low: 0.8 (0.5, 1.2) Med: 0.8 (0.6, 1.1) High: 0.9 (0.5, 1.8) <u>Follicular lymphoma</u>: Low: 0.9 (0.5, 1.5) Med: 1.3 (0.9, 1.8) High: 1.6 (0.7, 3.4) <u>Chronic lymphocytic leukemia</u>: Low: 1.1 (0.7, 1.8) Med: 0.9 (0.6, 1.2) High: 1.8 (0.9, 3.6)	High probability of exposure # cases 1-14 yrs: OR=0.7 (0.4, 1.5) 15 15-29 yrs: OR=1.9 (0.8, 4.3) 17 30-39 yrs: OR=2.8 (1.0, 7.8) 15 40+ yrs: OR=3.3 (0.3, 33) 3 % work time exposed: ≤5%: OR=1.6 (0.8, 3.2) 22 6-30%: OR=1.2 (0.6, 2.4) 20 >30%: OR=1.3 (0.4, 3.7) 8	High probability of exposure and Intensity level (ppm) # cases ≤5: OR=1.1 (0.4, 3.0) 8 5-75: OR=1.3 (0.8, 2.2) 33 >75: OR=2.2 (0.7, 6.7) 9
Vlaanderen 2013 Incidence 69,254 cases 346,270 controls 1961-2005	JEM Exposure tertiles (unexposed as referent)		Cumulative exposure tertiles, HR, #exposed cases: TCE # cases PCE # cases Benzene # cases 1: 1.01 (0.95, 1.07) 1,213 1.06 (0.94, 1.19) 346 0.99 (0.93, 1.06) 1,259 2: 0.93 (0.88, 1.00) 1,183 1.04 (0.93, 1.17) 337 1.01 (0.95, 1.07) 1,289 3: 0.97 (0.91, 1.03) 1,211 0.95 (0.84, 1.08) 292 0.97 (0.91, 1.04) 1,212		>90th percentile cumulative exposure: TCE: HR=0.95 (0.84, 1.06) 353 cases PCE: HR=1.04 (0.84, 1.29) 102 cases >90th percentile, intensity x freq exposed TCE: HR=0.96 (0.84, 1.09) 269 cases PCE: HR=1.23 (1.00, 1.52) 113 cases
<u>Dry Cleaning Workers Studies:</u>					
Blair 2003 Mortality 5,369 1948-1993	Dry Cleaning	12	Any exposure SMR=0.9 (0.5, 1.6)		
Lynge 2006 Incidence 187 cases 939 controls 1970-2001	Dry Cleaning	42	Unexposed as referent: RR=0.95 (0.65, 1.41)	Duration of employment (RR) 0-1 yr: 1.35 (0.44, 4.14) 5 cases 2-4 yrs: 0.61 (0.17, 2.21) 3 cases 5-9 yrs: 0.92 (0.49, 1.72) 14 cases ≥10 yrs: 0.66 (0.36, 1.22) 15 cases Unk: 1.47 (0.49, 4.47) 5 cases	

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Calvert 2011 Mortality 1,704 618 PCE-only 1,086 PCE-plus 1940-2004	Dry Cleaning (industry surveys, personal monitoring data, work history)	11 6 5	SMR=1.57 (0.78, 2.81) All SMR=2.46 (0.90, 5.36) PCE only SMR=1.10 (0.36, 2.56) PCE plus		
Selden 2011 Incidence 6,356 1985-2006	Dry Cleaning: PCE subcohort (plant survey, work history)	 33 15 18	Any exposure All: SIR=1.42 (0.98, 2.00) Men: SIR=2.02 (1.13, 3.34) Women: SIR=1.14 (0.68, 1.81)	Employment duration (years) (RRs) <1: 3.3 (1.6, 6.0) 10 cases 1-4: 1.0 (0.4, 2.1) 7 cases >4: 1.2 (0.7, 2.0) 16 cases	
Morton 2014 Incidence 17,471 cases 23,096 controls	Dry Cleaning	97	OR=1.02 (0.75, 1.38)		
't Mannetje 2015 Incidence 10,046 cases 12,025 controls 1988-2004	Dry cleaning Ever employed >10 years employment	 97 	Not a dry cleaner is referent: OR=0.92 (0.70, 1.20) OR=1.29 (0.74, 2.23)		
Benzene Workers Studies:					
Wang 2008 Incidence 601 cases 717 controls 1996-2000	Benzene (JEM)	120	OR=1.1 (0.9, 1.5)		Avg. Exposure Intensity: Low: OR=1.0 (0.7, 1.4) 80 cases Med-High: OR=1.5 (0.9, 2.4) 40 cases Med-High intensity & exp. probability: OR=1.4 (0.8, 2.4) 30 cases
Orsi 2010 Incidence 244 cases 436 controls 2000-2004	Benzene (JEM)	94 70 6	OR=1.0 (0.7, 1.5) >1ppm: OR=1.4 (0.9, 2.1) "pure benzene": OR=3.0 (0.8, 11)	Definite exp. /Duration of exposure: <5 yrs: OR=1.1 (0.6, 2.0) 23 cases 5-15 yrs: OR=0.8 (0.4, 1.4) 17 cases >15 yrs: OR=1.3 (0.8, 2.3) 26 cases	Average Intensity/definite exposure: Low: OR=1.2 (0.7, 2.2) 22 cases Medium: OR=0.9 (0.6, 1.5) 40 cases High: OR=2.6 (0.6, 11) 4 cases
Linet 2015 Incidence 73,789 exposed 35,504 unexposed 1972-1999	Benzene	 30 19 11	Any exposure: RR=3.9 (1.5, 13.2) Male: RR=3.6 (1.2, 15) Female: RR=4.6 (0.9, 87)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Stenehjem 2015 Incidence 24,917 1999-2011	Benzene (JEM)	61	Any exposure (RR): 1.49 (0.90, 2.48) B-cell NHL	Duration exposed (yrs), B-cell NHL # cases >0–5.49: RR=1.44 (0.77, 2.67) 22 5.5–12.9: RR=1.52 (0.81, 2.84) 19 ≥13: RR=1.54 (0.82, 2.90) 20	Cum. exposure, tertiles, B-cell NHL 1st: RR=1.44 (0.77, 2.69) 21 cases 2nd: RR=1.44 (0.76, 2.73) 19 cases 3rd: RR= 1.62 (0.87, 3.01) 21 cases
Bassig 2015 Incidence 73,087 1996-2009	Benzene (JEM)	24	Any exposure: RR=1.87 (1.19, 2.96)	Exposure Duration (years) 1-11: RR=1.44 (0.63, 3.31) 6 cases 12-21: RR=2.10 (1.01, 4.35) 8 cases >21: RR=2.07 (1.07, 4.01) 10 cases	Cumulative Exposure (tertiles) 1st RR=0.93 (0.29, 2.96) 3 cases 2nd RR=2.22 (1.12, 4.44) 9 cases 3rd RR=2.16 (1.17, 3.98) 12 cases
Vinyl Chloride Workers Studies:					
Carreón 2014 Mortality 1,874 1960-2007	Vinyl chloride	11	Any exposure: SMR=2.38 (1.19, 4.26)	Duration of employment (SRR) 0.16-<1.1 yrs: 3.6 (0.6, 22) 4 cases 1.1-<15 yrs: 1.5 (0.2, 14) 2 cases ≥15 yrs: 3.9 (0.4, 35) 3 cases	Vinyl chloride exposure duration (SRR) >0-<6 yrs: 0.5 (0.1, 2.6) 4 cases ≥6 yrs: 0.4 (0.1, 2.2) 4 cases

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Drinking Water Studies:					
Cohn 1994 Incidence 75 towns in NJ 1979-1987 841 cases, male 817 cases, female	TCE-contaminated municipal drinking water (sample data)	M F 841 817 272 226 78 87 216 186 67 48 26 24 34 35 12 9 4 6 24 27 9 6 3 6	Males 0.1-5 ppb: RR=1.28 (1.10, 1.48) >5 ppb: RR=1.20 (0.94, 1.52) 0.1-5 ppb: RR=1.25 (0.93, 1.69) >5 ppb: RR=1.59 (1.04, 2.43) 0.1-5 ppb: RR=1.54 (0.74, 3.20) >5 ppb: RR=1.72 (0.58, 5.08) 0.1-5 ppb: RR=1.73 (0.73, 4.11) >5 ppb: RR=1.92 (0.54, 6.81)	Females Total NHL: RR=1.02 (0.87, 1.20) RR=1.36 (1.08, 1.70) Intermediate Grade: NHL: diffuse large cell/reticulosarcoma: RR=0.95 (0.68, 1.34) RR=1.66 (1.07, 2.59) High Grade NHL (total): RR=1.04 (0.48, 2.30) RR=2.43 (0.97, 6.05) High Grade NHL: non-Burkitt's: RR=0.92 (0.36, 2.37) RR=3.17 (1.23, 8.18)	
	PCE-contaminated municipal drinking water (sample data)	841 817 235 187 119 121 216 186 61 39 26 31 34 35 9 5 2 11 24 27 7 3 2 9	Total NHL: 0.1-5 ppb: RR=1.25 (1.07, 1.46) >5 ppb: RR=1.10 (0.90, 1.35) Intermediate Grade: NHL: diffuse large cell/reticulosarcoma: 0.1-5 ppb: RR=1.23 (0.91, 1.67) >5 ppb: RR=0.91 (0.60, 1.39) High Grade NHL (total): 0.1-5 ppb: RR=1.11 (0.51, 2.41) >5 ppb: RR=0.41 (0.09, 1.76) High Grade NHL: non-Burkitt's: 0.1-5 ppb: RR=1.26 (0.51, 3.09) >5 ppb: RR=0.61 (0.14, 2.65)	RR=0.95 (0.81, 1.13) RR=1.08 (0.89, 1.32) RR=0.86 (0.60, 1.24) RR=1.21 (0.82, 1.80) RR=0.71 (0.26, 1.89) RR=2.66 (1.27, 5.60) RR=0.53 (0.15, 1.82) RR=2.74 (1.20, 6.26)	

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Bove 2014a (Camp Lejeune Marines/Navy) Mortality 154,932: Camp Lejeune 154,969: Camp Pendleton 1979-2008	VOC contaminated drinking water (modeled) vs U.S. population vs. Camp Pendleton	58	SMR=0.68 (0.52, 0.88) HR=0.81 (0.56, 1.18)	—	—
Bove 2014b (Camp Lejeune Civilian workers) Mortality 4,647: Camp Lejeune 4,690: Camp Pendleton 1979-2008	VOC contaminated drinking water U.S. population vs. Camp Pendleton	5	SMR=0.60 (0.19, 1.40) HR=0.83 (0.26, 2.67)		

* Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.

** One included study did not report the number of exposed cases. The rest of the included studies reported a total of 532 exposed cases.

Δ Two of the included studies did not report the number of exposed cases. The rest of the included studies reported a total of 228 exposed cases.

α "Significant evidence for between study heterogeneity…." (quoted from Vlaanderen et al. 2011).

Ψ Included in the Karami et al. 2013, EPA and Mandel et al. meta-analyses for TCE exposure. Included in the table for PCE exposure information.

£ Included in the Karami et al. 2013, EPA and Mandel et al. meta-analyses. Included in the table because of information on employment duration and exposure lag time.

€ Included in the Karami et al. 2013 and EPA meta-analyses. Included in the table because of information on exposure intensity (men only; there were small number of cases among women) and cumulative exposures.

+ Included in the Karami et al. 2013 meta-analysis. Included in the table for PCE information and for exposure duration for both TCE and PCE.

® Included in the Karami et al. 2013 and EPA meta-analyses for TCE exposure. Included in the table for PCE and benzene exposure information.

[¶] Included in the Cocco 2013 study but provided additional information on PCE and benzene .
RR: Risk Ratio
OR: Odds Ratio
SMR: Standardized Mortality Ratio
SIR: Standardized Incidence Ratio
95% CI: 95% Confidence Interval
sRR or mRR: summary risk ratio or meta-analysis risk ratio
HR: Hazard Ratio
JEM: Job-exposure matrix
I: Incidence; M: mortality
VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)
Urine TCA: urine levels of trichloroacetic acid, a metabolite of TCE.
Note: Boffetta et al. 2003 meta-analysis for vinyl chloride is not included in the table because it combined NHL and multiple myeloma.

Summary of EPA, IARC and NTP reviews of TCE, PCE, or benzene and NHL:

EPA Toxicological Review of TCE (EPA 2011): "The human evidence of carcinogenicity from epidemiologic studies of TCE exposure is strong for NHL but less convincing than for kidney cancer…." "Associations observed in epidemiologic studies of lymphoma and TCE exposure suggest a causal relation between TCE exposure and NHL."

IARC review of TCE (IARC 2014) concluded that there was a positive association between TCE and NHL. In particular, the cohort studies of biologically monitored workers in the Nordic countries "show evidence of modestly increased risk for non-Hodgkin lymphoma" (p. 185). The meta-analyses were consistent in finding that TCE exposure increased the risk of NHL. Higher risks were observed in the cohort studies compared to the case-control studies. This may be due to better exposure assessment in the cohort studies.

NTP Monograph on TCE (NTP 2015): "Overall, there is some evidence of an association between exposure to trichloroethylene and NHL based on findings of a modest increase in risk of NHL in several studies with different study designs and in different populations, although the strength of the evidence varied." (p. 132-33)"

EPA Toxicological Review of PCE (EPA 2012): "The results from the collection of studies pertaining to non-Hodgkin lymphoma indicate an elevated risk associated with tetrachloroethylene exposure. The results from five cohort studies that used a relatively high quality exposure-assessment methodology generally reported relative risks between 1.7 and 3.8 (Calvert et al. 2011; Seldén and Ahlborg, 2011; Radican et al. 2008; Boice et al. 1999; Anttila et al. 1995) and support an association with tetrachloroethylene. The studies with tetrachloroethylene-specific exposure measures and exposure-response analysis (based on intensity, duration, or cumulative exposure) (Seidler et al. 2007; Miligi et al. 2006; Boice et al. 1999) provide further support for an association, reporting higher non-Hodgkin lymphoma risks in the highest exposure category, with the strongest evidence from the large case-control study in Germany, in which a relative risk of 3.4 (95% CI: 0.7, 17.3) was observed in the highest cumulative exposure category (trend p-value = 0.12) (Seidler et al. 2007). Lynge et al. (2006) distinguished dry cleaners from other workers but used an approach with greater potential for misclassification because exposure was assigned only for jobs held in 1970. This study did not report an association between dry cleaners and non-Hodgkin lymphoma, nor did risk estimates increase with exposure duration. Effect estimates in studies with broader exposure assessments showed a more variable pattern.... Confounding by lifestyle factors are unlikely explanations for the observed non-Hodgkin lymphoma results because common behaviors, such as smoking and alcohol use, are not strong risk factors for non-Hodgkin lymphoma....."

IARC review of benzene (IARC 2012): In its review, IARC observed that a positive association existed between exposure to benzene and non-Hodgkin lymphoma but concluded that there was limited evidence in humans for a causal association of benzene with NHL. However, IARC also concluded: "...the biological plausibility of benzene as a cause of lymphoproliferative disorders has been strengthened in recent years. There are additional studies demonstrating that benzene produces lymphomas in laboratory animals...." "Multiple studies show that it produces genotoxicity in the lymphocytes of exposed humans. Accordingly, there is considerable support for the notion that it is biologically plausible for benzene to cause human lymphatic tumours."

ATSDR Assessment

In the assessment of the evidence for causation, ATSDR placed high weight on assessments conducted by EPA, NTP and IARC as well as the meta-analyses. High weight was also given to a study that was considered of moderate or high utility by the NTP, evaluated NHL subgroupings, or provided mechanistic information. Our assessment of the epidemiological evidence considered some of the viewpoints associated with Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if ≤1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding.

TCE

NTP (NTP 2015) found that TCE exposure increased the risks for NHL among all of the three studies they considered of high or moderate utility for evaluation of NHL (Cocco et al. 2013, Hansen et al. 2013, Radican et al. 2008). NTP considered the pooled InterLymph analysis study by Cocco et al. 2013 to be the most informative study because it evaluated NHL subtypes and conducted a good exposure assessment. ATSDR agrees with NTP that this study is highly informative because of its evaluation of NHL subtypes. This study found an increased risk of NHL (all types) among workers with high probability of exposure to TCE (OR=1.4, 95% CI: 0.9, 2.1) as well as increased risk for the NHL subtypes, follicular lymphoma (OR=1.6, 95% CI: 0.7, 3.4) and chronic lymphocytic leukemia (OR=1.8, 95% CI: 0.9, 3.6). ATSDR concurs with EPA that the occupational epidemiological studies provide strong evidence of causation for TCE and NHL. The meta-analyses by EPA (Scott and Jinot 2011) and Karami et al. 2013 summarize the findings from these studies and strengthen the evidence that TCE causes NHL. The strongest findings in these meta-analyses were contributed by the cohort studies. Karami et al. 2013 reported no between-study heterogeneity and no evidence of publication bias for the cohort studies included in the meta-analysis. The EPA meta-analysis reported low between-study heterogeneity in the analysis of higher TCE exposure.

Animal and mechanistic information for TCE: "Severe immune dysregulation, whether from immunosuppression, inflammation, or autoimmune disease, is associated with an increased risk of NHL. Thus, it is biologically plausible that the mode of action of trichloroethylene-induced NHL could involve altered immunity. … Although few applicable studies were conducted in humans, the available data provide evidence that trichloroethylene can alter the immune system based on some studies finding an association between markers of immune modulation and other studies showing an association with autoimmune disease (e.g., systemic sclerosis). … However, the available data are insufficient to demonstrate that immunomodulation is operant as a mode of action for trichloroethylene-induced NHL." (NTP 2015, p. 148). Evidence from animal studies indicates that TCE exposure causes immunomodulation including autoimmune disease and immunosuppression. Both autoimmune disease and immunosuppression are associated with NHL. Studies conducted of Chinese factory workers exposed to TCE have observed alterations in immune function markers that have been associated with an increased risk of NHL, indicating that the associations observed between TCE and NHL are biologically plausible (Bassig et al. 2013). In a recent study of the cohort of Chinese factory workers, total lymphocyte counts decreased with increasing exposures to TCE. Similar exposure-response trends

were observed for $CD4^+$ T cells, $CD8^+$ T cells B cells and NK cells (Bassig et al. 2016). The study concluded that these results provided evidence that TCE exposure can lead to immunosuppresssion, which is associated with an increased risk of NHL.

Exposure-Response: An increased risk with longer duration of exposure was observed in the Mandel et al. 2006 meta-analysis and for cohort studies in the Karami et al. 2013 meta-analysis. An increased risk with longer exposure duration was also found in the Raaschou-Nielsen et al. 2003 and Cocco et al. 2013 studies. An increased risk with higher TCE cumulative exposure was found in the Scott and Jinot 2011 meta-analysis and the Cocco et al. 2013 study. Increased risk with higher exposure intensity was found in the Karami et al. 2013 meta-analysis for case-control studies but not cohort studies. Two of the meta-analyses of TCE suggest that "low intensity" exposures can also result in an elevated risk of NHL (Mandel et al. 2006, Karami et al. 2013).

Conclusion: Based on the meta-analyses, the study of NHL subtypes (Cocco et al. 2013), and the mechanistic evidence that TCE causes immunosuppression which is a risk factor for NHL, ATSDR concludes that there is **sufficient evidence for causation for TCE and NHL.**

PCE

No meta-analyses have been conducted for PCE and NHL. The findings for PCE and NHL are mixed. Among the dry cleaning worker studies, Calvert et al. 2011 and Selden et al. 2011 found elevated risks for NHL, although virtually all the elevated risk in the latter study occurred among male workers. The study by 't Mannetje et al. 2015 observed no elevated risk for ever exposed but obtained an OR of 1.29 (95% CI: 0.74, 2.23) for those with greater than 10 years of employment as a dry cleaning worker. The other dry cleaning worker studies (Blair et al. 2003; Morton et al. 2014) either found no elevation in risk or a risk near the null; and one study found no elevation in risk except among those with ≤1 year of employment and with unknown duration of employment (Lynge et al. 2006). Four cohort studies (Antilla et al. 1995, Radican et al. 2008, Lipworth et al. 2011, Silver et al. 2014) and two case-control studies (Seidler et al. 2007, Christensen et al. 2013) of PCE exposed workers also found elevated risks for NHL. In the Seidler et al. 2007 case-control study, only PCE exposed workers in the 90^{th} percentile of cumulative exposure had elevated risks for NHL and the B-cell NHL subtype. The NJ drinking water study (Cohn et al. 1994) found elevated risks for NHL and specific NHL grades, but only among women. Risks were not elevated in the Camp Lejeune mortality studies (Bove et al. 2014a, b).

In its toxicological review of PCE, EPA concluded that the findings from the cohort studies of PCE workers and two of the cohort studies of dry cleaning workers provided support for an association between PCE and NHL (EPA 2012). On the other hand, the IARC review of PCE stressed the lack of consistent findings across studies and the small numbers of exposed cases in many of the studies (IARC 2014). The lack of consistent findings could be due to non-differential exposure misclassification bias. The small number of exposed cases in some of the cohort studies that evaluated NHL mortality would be expected since NHL is highly survivable with a 5-year survival percentage of about 70%. ATSDR agrees with EPA's conclusion that the findings from the positive cohort and case-control studies are unlikely to be affected by confounding due to lifestyle factors, since these factors are not strong risk factors for NHL and are unlikely to be associated with PCE exposure status. ATSDR concludes that the epidemiological evidence for PCE and NHL, although weak, is sufficient to classify the causal association as at least equipoise.

Conclusion: Based on the epidemiological evidence, ATSDR concludes that there is **equipoise and above evidence for causation for PCE and NHL.**

Benzene

Three meta-analyses of benzene and NHL have been conducted. The Steinmaus et al. 2008 meta-analysis found an elevated summary risk ratio when 16 case-control and 6 cohort studies were evaluated. The summary risk ratio (sRR) increased from 1.22 (95% CI: 1.03, 1.46) to 2.12 (95% CI: 1.11, 4.02) when the analyses were restricted to studies that did not use self-reported exposure information. The meta-analysis attempted to address the healthy worker bias effect that can arise when SMRs are calculated. The approach involves replacing the SMR with the mortality odds ratio which is computed by comparing NHL ("cases") to all other causes of death ("controls") on their benzene exposures and assuming that the healthy worker effect bias will be similar across cases and controls. This approach resulted in a slight increase in the sRR for the 6 studies that did not use self-reported exposure information, from an sRR of 2.12 (95% CI: 1.11, 4.02) to an sRR of 2.26 (95% CI: 1.29, 3.97).

Two meta-analyses were published after the IARC workgroup met in 2009 (IARC 2012). The Kane 2010 meta-analysis included two studies (cancer registry, death certificates) that should be considered surveillance efforts that based their exposure assessments on the occupation listed on the cancer registration or death certificate. The summary RR was 1.11 (95% CI: 0.94, 1.30) based on a total of 24 studies. The Vlaanderen et al. 2011 meta-analysis found an elevated sRR only when the analysis was restricted to the 6 cohort studies with quantitative exposure assessment (sRR=1.27, 95% CI: 0.90, 1.79). Restricting the analyses to these 6 cohort studies removed the between-study heterogeneity that was present when the analyses were not restricted to studies with quantitative exposure assessments.

The Vlaanderen et al 2011 meta-analysis was mostly based on mortality studies. This was a limitation since NHL is highly survivable with a 5-year survival percentage of about 70%. The three large cohort studies published after the Vlaanderen et al. 2011 meta-analysis evaluated NHL incidence. These three cohort studies observed higher risks for benzene exposures and NHL than those observed in the Vlaanderen et al. 2011 meta-analysis (Linet et al. 2015, Stenehjem et al. 2015, Bassig et al. 2015). The Stenehjem et al. 2015 study assessed exposures using a semi-quantitative JEM and observed monotonic exposure-response trends for B-cell NHL and exposure duration and cumulative exposure. The Bassig et al. 2015 study observed non-monotonic exposure-response trends. The Bassig study's exposure assessment was particularly comprehensive, using an industry JEM and an occupation JEM calibrated with short-term area air benzene exposure measurements conducted in the Shanghai factories.

Animal and mechanistic information for Benzene: "…, there are at least two probable mechanisms by which exposure to benzene could enhance the incidence of lymphoma, i.e. by inducing chromosome rearrangements associated with NHL, and through immunosuppression leading to decreased immunosurveillance. Benzene is well known to produce multiple cytogenetic abnormalities in lymphocytes…. Further, benzene induces specific chromosomal changes associated with NHL in human lymphocytes…." (IARC 2012). Benzene has also produced lymphomas in animal studies (IARC 2012). In a recent study of the cohort of Chinese factory workers, benzene exposure was associated with

alterations in lymphoid cell types and B-cell activation markers indicative of immunosuppresssion that could result in an increased risk of NHL (Bassig et al. 2016).

Conclusion: Although IARC concluded that the human evidence for causation for benzene and NHL was "limited", three recent large cohort studies have found positive associations. Based on the recent epidemiological evidence and the supporting evidence from mechanistic and animal studies, ATSDR concludes that there is **sufficient evidence for causation for benzene and NHL**.

Multiple Myeloma

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Alexander 2006 **Meta-analysis**	TCE	62	sRR = 1.05 (0.80, 1.38) 7 studies (4 I, 3 M)	—	—
Karami 2013 **Meta-analysis**	TCE	148	sRR = 1.07 (0.86, 1.34) 8 cohort studies (4 incidence (I), 4 mortality (M)) & 2 case-control studies (2 I)		—
Infante 2006 **Meta-analysis**	Benzene	22	sRR = 2.13 (1.31, 3.46) 7 cohort studies	—	—
Vlaanderen 2011 **Meta-analysis**	Benzene	284 37 28	Quantitative & qualitative exposure assessment: mRR=1.12 (0.98, 1.27) 26 cohort studies Quantitative to some industrial hygiene sampling: mRR=1.15 (0.74, 1.79) 9 cohort studies Quantitative exposure assessment: mRR=1.48 (0.96, 2.27) 8 cohort studies (2 I, 6 M)		
Cohort Studies					
Anttila 1995 Incidence 3,089 TCE workers 849 PCE workers 1967-1992	TCE (urine TCA)				Urine TCA (µmol/L) # cases <100: SIR=1.48 (0.18, 5.35) 2 ≥100: SIR=2.41 (0.29, 8.71) 2
Radican 2008[6] Mortality 14,455 1953-2000	Aircraft maintenance TCE (JEM)	25 19 6	Any TCE exposure: HR=1.35 (0.62, 2.93) HR=1.08 (0.43, 2.71), men HR=2.37 (0.67, 8.44), women	TCE cumulative exposure (unit-yrs): Men (HR) # cases >0-5: 0.7 (0.2, 2.3) 5 >5-25: 1.6 (0.5, 4.7) 7 >25: 1.2 (0.4, 3.5) 7 Women (HR) # cases >0-5: 2.2 (0.4, 12) 2 >5-25: 2.8 (0.3, 25) 1 >25: 2.4 (0.5, 11) 3	TCE exposure intensity Men HR # cases Low, intermittent: 1.0 (0.4, 2.7) 13 Low, continuous: 1.2 (0.4, 3.4) 10 Peak, infrequent: 1.8 (0.5, 5.8) 5 Peak, frequent: 1.3 (0.5, 3.6) 10 Women HR # cases Low, Intermittent: 4.3 (1.1, 16) 5 Low, Continuous: 1.7 (0.2, 15) 1 Peak, Infrequent: 3.2 (0.4, 29) 1 Peak, Frequent: 1.9 (0.4, 8.7) 3
	PCE (JEM)	3 2	HR=1.7 (0.4, 6.9) men HR=7.8 (1.4, 43.1) women		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Lipworth 2011 Mortality 5,443 (TCE) 5,830 (PCE) 1960-2008	Aircraft manufacturing TCE (JEM) PCE (JEM)	 23 14	Any exposure: SMR=1.21 (0.76, 1.81) SMR=1.07 (0.58, 1.79)	Years exposed (RRs): TCE <1: 0.70 (0.31, 1.58) 8 cases 1-4: 1.45 (0.68, 3.09) 10 cases >4: 0.67 (0.25, 1.83) 5 cases PCE <1: 0.87 (0.30, 2.51) 4 cases 1-4: 1.14 (0.46, 2.82) 6 cases >4: 0.34 (0.08, 1.49) 2 cases	—
Hansen 2013 Incidence 5,553 Finland:1967-2004 Sweden: 1958-2003 Denmark: 1968-2008	TCE (urine TCA was used to identify workers ever exposed to TCE)	4 4 8	Men: SIR= 0.47 (0.13, 1.20) Women: SIR=1.04 (0.29, 2.67) All: SIR=0.65 (0.28, 1.27)	—	—
Silver 2014 Mortality 34,494 1969-2009	Microelectronics plant TCE (JEM) PCE (JEM)	36	5 exposure-years, cumulative exposure: HR=1.18 (0.70, 1.99) HR=0.04 (0.00, 59.7)	—	—
Buhagen 2016 Incidence 997 males 1960-2010	Train maintenance TCE (union employment list)	8	SIR=0.8 (0.4, 1.7)		
Case-control Studies					
Seidler 2007¶ Incidence 75 cases 710 controls	TCE Benzene	10 13			Cumulative exposure (ppm*yrs) **TCE** >0-≤8.6: OR=0.5 (0.2, 1.9) 3 cases >8.6-≤130: OR=1.0 (0.4, 2.7) 6 cases >130: OR=0.7 (0.1, 5.5) 1 cases **Benzene** >0-≤8.6: OR=1.0 (0.4, 2.4) 6 cases >8.6-≤130: OR=0.7 (0.2, 2.0) 4 cases >130: OR=1.8 (0.5, 6.8) 3 cases

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Costantini 2008 Incidence 263 cases 1,100 controls 1991-1993	TCE Benzene	14 22		Medium/High intensity Exposure duration (yrs.) (OR): TCE ≤15: 0.5 (0.1, 2.3) 2 cases >15: 1.3 (0.3, 5.9) 3 cases Benzene ≤15: 0.8 (0.3, 2.2) 9 cases >15: 4.1 (0.8, 20) 5 cases	Exposure Intensity (ORs) TCE Very low/Low: 1.5 (0.7, 3.5) 9 cases Medium/High: 0.9 (0.3, 2.4) 5 cases Benzene Very low/Low: 0.6 (0.3, 1.5) 8 cases Medium/High: 1.9 (0.9, 3.9) 14 cases
Gold 2011[£] Incidence 180 cases 481 controls 2000-2002	TCE (JEM) PCE (JEM)	66 43 29 16	All: OR=1.4 (0.9, 2.1) Likely exposed: OR= 1.7 (1.0, 2.7) All: OR=1.4 (0.9, 2.4) Likely exposed: OR=1.5 (0.8, 2.9)	Likely exposed, exposure duration 1-4 yrs: OR=0.9 (0.3, 2.4) 6 cases 5-7 yrs: OR=1.3 (0.5, 3.6) 6 cases 8-24 yrs: OR=2.5 (1.2, 5.1) 20 cases >24 yrs: OR=1.9 (0.8, 4.5) 11 cases 1-4 yrs: OR=0.9 (0.2, 3.5) 3 cases 5-7 yrs: OR=2.0 (0.4, 9.2) 3 cases 8-24 yrs: OR=1.3 (0.3, 4.6) 4 cases >24 yrs: OR=2.1 (0.7, 6.8) 6 cases	Likely exposed, cum. exp. quartile, 10yr exposure lag 1: OR=1.1 (0.4, 2.9) 6 cases 2: OR=1.6 (0.7, 3.5) 11 cases 3: OR=1.4 (0.5, 3.8) 6 cases 4: OR=2.3 (1.1, 5.0) 18 cases 1: OR=0.4 (0.0, 3.2) 1 case 2: OR=0.5 (0.1, 4.7) 1 case 3: OR=1.7 (0.5, 6.5) 4 cases 4: OR=4.1 (1.4, 12) 10 cases
Vlaanderen 2013[#] Incidence 35,534 cases 177,670 controls 1961-2005	JEM Exposure tertiles (unexposed as referent)		Cumulative exposure tertiles, HR, # cases: TCE # cases PCE # cases Benzene # cases 1: 0.93 (0.84, 1.03) 468 0.99 (0.83, 1.18) 149 1.01 (0.92, 1.11) 584 2: 0.92 (0.84, 1.01) 574 0.93 (0.78, 1.12) 140 1.00 (0.92, 1.09) 663 3: 0.96 (0.88, 1.06) 541 0.98 (0.82, 1.17) 148 0.93 (0.85, 1.02) 577		>90th percentile cumulative exposure: TCE: HR=1.01 (0.84, 1.22) 132 cases PCE: HR=1.15 (0.88, 1.51) 64 cases >90th percentile, intensity x freq exposed TCE: HR=1.03 (0.88, 1.22) 174 cases PCE: HR=1.18 (0.87, 1.59) 53 cases
Dry Cleaning Workers Studies					
Blair 2003 Mortality 5,369 1948-1993	Dry cleaning	7	Any exposure: SMR=0.8 (0.3, 1.6)		
Selden 2011 Incidence 9,440 1985-2006	Dry Cleaning & Laundry Workers (plant survey, work history)	11	SIR=0.79 (0.39, 1.41)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Benzene Workers Studies					
Orsi 2010 Incidence 2000-2004 56 cases, 313 controls	Benzene (JEM)	28 19	Any exposure: OR=1.3 (0.7, 2.5) Benzene >1ppm: OR=0.9 (0.5, 1.9)		
Cocco 2010 Incidence 176 cases 1,589 controls 1998-2004	Benzene (questionnaires, workplace inspections)	16	Ever/never exposed: OR=0.9 (0.5, 1.6)	–	Low: OR=0.7 4 cases Medium: OR=0.4 2 cases High: OR=1.4 10 cases (Confidence intervals were not provided.)
Stenehjem 2015 Incidence 24,917 1999-2011	Benzene (offshore oil industry workers) (JEM)	13	Ever/never exposed: RR = 1.64 (0.55, 4.89)	Years exposed # cases >0–5.49: RR = 1.31 (0.32, 5.35) 4 5.5–<13: RR = 2.05 (0.58, 7.24) 5 ≥ 13: RR = 1.65 (0.42, 6.51) 4	Cumulative exposure (tertiles) 1st: RR=0.99 (0.22, 4.52) 3 cases 2nd: RR=1.14 (0.26, 5.10) 3 cases 3rd: RR=3.25 (1.00, 10) 7 cases
Drinking Water Studies					
Bove 2014a (Camp Lejeune Marines/Navy) Mortality 154,932: Camp Lejeune 154,969: Camp Pendleton 1979-2008	VOC contaminated drinking water (modeled) vs U.S. population vs. Camp Pendleton	17	SMR = 1.05 (0.61-1.69) HR = 1.68 (0.76, 3.72)	Duration of exposure # cases 1–3 months: OR=2.8 (0.7, 12) 3 4–12 months: OR=2.5 (0.7, 7.9) 5 >12 months: OR=0.8 (0.2, 2.9) 4	Modeled TCE cumulative exposure (unexposed as referent): Very low: HR=1.3 (0.5, 3.6) Low to high: HR=1.6 (0.7, 3.7)
Bove 2014b (Camp Lejeune Civilian workers) Mortality 4,647: Camp Lejeune 4,690: Camp Pendleton 1979-2008	VOC contaminated drinking water (modeled) vs U.S. population vs. Camp Pendleton	6	SMR=1.50 (0.55, 3.28) HR =1.84 (0.45, 7.58)	–	Modeled TCE cumulative exposure: (<median as referent): ≥median: HR=0.6 (0.1, 3.2) (4 of the 6 cases had >median average exposure to TCE)

* Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.

€ Included in the Karami et al. 2013 meta-analysis. Included in the table because of information on TCE exposure intensity and cumulative exposures, and information on PCE exposure.

¶ Not included in the meta-analyses of TCE or benzene.

£ Included in the Karami et al. 2013 meta-analysis. Included in the table because of information on exposure duration and cumulative exposure.

The Vlaanderen 2013 study did not provide findings for >90th percentile cumulative benzene exposure or >90th percentile intensity x frequency exposure to benzene.

RR: Risk Ratio

OR: Odds Ratio

SMR: Standardized Mortality Ratio

SIR: Standardized Incidence Ratio

95% CI: 95% Confidence Interval

mRR: meta-analysis risk ratio

sRR: summary risk ratio from the meta-analysis

HR: Hazard Ratio

JEM: Job-exposure matrix

I: Incidence: M: mortality

VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)

Urine TCA: urine levels of trichloroacetic acid, a metabolite of TCE.

Note: Boffetta et al. 2003 meta-analysis for vinyl chloride is not included in the table because it combined NHL and multiple myeloma.

Summary of EPA's review of PCE and multiple myeloma

EPA Toxicological Review of PCE (EPA 2012): "For non-Hodgkin lymphoma and multiple myeloma, the presence of higher relative risk estimates in studies with better exposure-assessment methodologies and evidence of an exposure-response trend in one or more studies provide the basis for considering the collection of studies as supportive of a role of tetrachloroethylene as a likely carcinogen."

ATSDR Assessment

In the assessment of the evidence for causation, ATSDR placed high weight on assessments conducted by EPA and IARC as well as the meta-analyses. High weight was also given to a study that provided mechanistic information. Our assessment of the epidemiological evidence considered some of the viewpoints associated with Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if ≤1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding.

TCE

The meta-analyses indicate that TCE exposures are associated with risks near the null. However, elevated risks for multiple myeloma incidence were observed for TCE in a large case-control study that evaluated cumulative exposure and duration of exposure (Gold et al. 2011). Odds ratios of 1.7 (95% CI: 1.0, 2.7) and 2.3 (95% CI: 1.1, 5.0) were observed for those likely exposed to TCE and those with TCE cumulative exposure in the top quartile, respectively (Gold et al. 2011). Odds ratios of 2.5 (95% CI: 1.2, 5.1) and 1.9 (95%CI: 0.8, 4.5) were observed for those likely exposed to TCE for 8 – 24 years and for >24 years, respectively (Gold et al 2011). To minimize exposure misclassification bias in this study, occupation-specific and industry-specific JEMs based on extensive information on chlorinated solvent use in industry were applied to each individual's detailed work histories (Gold et al. 2011).

In one cohort study, elevated mortality risks for multiple myeloma were observed mostly for female workers although the number of exposed cases was small (Radican et al. 2008). Other cohort studies observed relative risks of about 1.20 (Lipworth et al. 2011, Silver et al. 2014) or a much higher risk based on very few exposed cases (Anttila et al. 1995). Three cohort studies found no elevation in risk (Hansen et al. 2013, Buhagen et al. 2016 and Seidler et al. 2007) but were based on small number of exposed cases. One large case-control study observed no elevation in risk (Vlaanderen et al. 2013). However, the authors of this study acknowledged that the exposure assessment likely resulted in considerable exposure misclassification bias due to reliance on census data to ascertain work history (which provides only a "snapshot" of the work history and uses broad job categories) and a generic JEM.

The Camp Lejeune mortality studies found elevated risks for multiple myeloma mortality, which is noteworthy given that multiple myeloma is a disease of older populations (median age=69 for diagnosis, and 75% are diagnosed after age 55) and the Camp Lejeune cohorts were relatively young at the end of the studies: Marines/Navy personnel, median age=49, years, <3% aged 55 or older; and civilian workers, median age=58, over 70% under the age of 65 (Bove et al. 2014a, 2014b). For Marines and Navy personnel at Camp Lejeune, the exposure-response analyses were limited by small numbers of exposed cases but elevated risks were observed with increasing cumulative exposure and for exposure durations of 1-3 and 4-12 months but not for a duration of more than a year (Bove et al. 2014a).

Animal and mechanistic Information: Evidence from animal data indicates that TCE causes autoimmune disorders (Chiu et al. 2013). In humans, TCE has been associated with systemic sclerosis (see section on systemic sclerosis later in this report). In a recent meta-analysis (McShane et al. 2014), any autoimmune condition was associated with subsequent risk of multiple myeloma (pooled RR=1.13, 95% CI: 1.04, 1.22). Systemic sclerosis had a pooled RR of 1.28 (0.66, 2.48) for multiple myeloma based on 3 studies. A much stronger association was observed between systemic sclerosis and subsequent risk of Monoclonal Gammopathy of Undetermined Significance (MGUS), a precursor to multiple myeloma, with a pooled RR of 4.87 (2.49, 9.54) based on two studies. In one of these two studies, based on patients identified in the U.S. Veterans Affairs (VA) Patient Treatment File (inpatient discharge data from VA hospitals) from 1969 to 1996, the RRs for systemic sclerosis and multiple myeloma and MGUS were 2.41 (1.08, 5.36) and 4.21 (1.89, 9.38), respectively (Brown et al. 2008). In general, systemic sclerosis is associated with hematopoietic cancers including NHL and leukemia (Onishi et al. 2013; Zhang et al. 2013). One hypothesis is that chronic stimulation of the immune system may lead to multiple myeloma. Another hypothesis is that the dysfunctional immune system found in autoimmune diseases may allow malignant clones to exist, escape and persist (McShane et al. 2014). Premature aging of the immune system associated with autoimmune diseases could reduce the ability to distinguish "self" and "foreign" antigens.

Conclusion: ATSDR concludes that the epidemiological evidence for TCE and multiple myeloma is insufficient by itself to reach equipoise. However, there is mechanistic information that provides support for a causal association. Evidence from animal studies indicates that TCE exposure causes immunomodulation including autoimmune disease. In human studies, TCE has been associated with the autoimmune disease, systemic sclerosis. Autoimmune disorders, including systemic sclerosis are associated with multiple myeloma. Combining the epidemiological and mechanistic evidence, ATSDR concludes that there is **equipoise and above evidence for causation for TCE and multiple myeloma.**

PCE

No meta-analyses have been conducted that evaluated PCE exposure and multiple myeloma. In one large case-control study, an elevated risk for multiple myeloma was observed among those most likely exposed to PCE (OR=1.5, 95% CI: 0.8, 2.9). Although no elevation in risk was observed in the first two quartiles of cumulative PCE exposure (based on 1 case in each quartile), those in the upper two quartiles

had ORs of 1.7 (95% CI: 0.5, 6.5) and 4.1 (95% CI: 1.4, 12.0), respectively (Gold et al. 2011). Elevated ORs were also observed among those with exposure durations ≥5 years although the trend was not monotonic. A cohort mortality study observed elevated risks among men and women but it was based on ≤3 exposed cases (Radican et al. 2008). Another mortality cohort study observed an SMR near the null, with an elevated risk for those with 1-4 years of exposure but no elevation in risk among those exposed for more than four years (Lipworth et al. 2011). A third mortality cohort study did not observe an elevated risk (Silver et al. 2014). Two cohort studies of dry cleaning workers, one evaluating mortality (Blair et al. 2003) and the other evaluating incidence (Selden et al. 2011) observed no elevation in risk.

ATSDR concludes that the epidemiological evidence is mixed and inadequate to determine whether a causal association exists for PCE and multiple myeloma. There is also a lack of animal or mechanistic information.

Conclusion: ATSDR concludes that there is insufficient information to determine whether a causal association exists for PCE and multiple myeloma. Therefore ATSDR concludes that there is **below equipoise evidence for causation for PCE and multiple myeloma**.

Benzene

The IARC (IARC 2012, Monograph 100F) concluded that a positive association was observed for benzene exposure and multiple myeloma. The Infante et al. 2006 meta-analysis supports this conclusion. The IARC review was completed before the Vlaanderen et al. 2011 meta-analysis and the recent study of Norwegian offshore oil industry workers (Stenehjem et al. 2015) which provided additional evidence for an association between benzene exposure and multiple myeloma. The latter study found an exposure-response trend for cumulative exposure although based on a small number of exposed cases (Stenehjem et al. 2015). There was also a non-monotonic trend for exposure duration in this study. The meta-analysis by Vlaanderen et al 2011 observed a summary risk ratio of 1.12 (95% CI: 0.98, 1.27) based on 26 cohort studies, however the summary risk ratio increased to 1.48 (95% CI: 0.96, 2.27) when the analysis was restricted to cohort studies with quantitative exposure assessments.

Conclusion: ATSDR concludes that there is **equipoise and above evidence for causation for benzene and multiple myeloma** based on the results of the meta-analyses and the recent study of Norwegian offshore oil industry workers.

Adult Leukemias*

Reference, type of cancer data, total # of subjects, follow-up period	Exposure** (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Boffetta 2003 **Meta-analysis**	Vinyl chloride	53	Summary SMR=0.91 (0.69, 1.21) 2 multi-center cohort mortality studies		
Alexander 2006 **Meta-analysis**	TCE	131 (?)***	sRR = 1.11 (0.93, 1.32) 7 studies (3 I, 3 M, 1 not reported)	—	—
Karami 2013 **Meta-analysis**	TCE	188 (?)****	sRR = 1.10 (0.94, 1.28) 9 cohort studies (3 incidence, 6 mortality); 1 case-control study (mortality) CLL/SLL: summary RR=1.19 (0.73, 1.96) 5 studies (2 cohort mortality studies; 3 case-control incidence studies)		
Khalade 2010 **Meta-analysis**	Benzene	Not reported	Leukemia: sRR = 1.40 (1.23, 1.57) 15 studies (12 cohort, 3 case-control) AML: sRR = 1.38 (1.15, 1.64) 8 studies CML: sRR = 1.05 (0.83, 1.34) 6 studies CLL: sRR = 1.31 (1.09, 1.57) 10 studies		Cumulative exposure (sRR) # cases Leukemia <40 ppm-yrs: 1.64 (1.13, 2.39) 66 40-99 ppm-yrs: 1.90 (1.26, 2.89) 44 ≥100 ppm-yrs: 2.62 (1.57, 4.39) 33 AML <40 ppm-yrs: 1.94 (0.95, 3.95) 18 40-99 ppm-yrs: 2.32 (0.91, 5.94) 8 ≥100 ppm-yrs: 3.20 (1.09, 9.45) 12 CLL <40 ppm-yrs: 1.83 (0.75, 4.48) 13 40-99 ppm-yrs: 1.67 (0.86, 3.24) 15 ≥100 ppm-yrs: 3.50 (0.90, 13.2) 9
Vlaanderen 2011 **Meta-analysis**	Benzene	217 217 108 95 71 47 47 11 11 5 111 111 61 53 43	AML Quantitative & qualitative exposure assessment: mRR=1.68 (1.35, 2.10) 21 studies Quantitative to some industrial hygiene sampling: mRR=1.73 (1.26, 2.38) 10 studies Quantitative or semi-quantitative estimates: mRR=1.82 (1.25, 2.66) 9 studies Quantitative exposure assessment: mRR=2.32 (1.55, 3.47) 6 studies (2 incidence, 4 mortality) ALL Quantitative & qualitative exposure assessment: mRR=1.44 (1.03, 2.02) 17 studies Quantitative to some industrial hygiene sampling: mRR=1.26 (0.50, 3.16) 4 studies Quantitative or semi-quantitative estimates: mRR=1.26 (0.50, 3.16) 4 studies Quantitative exposure assessment: mRR=2.80 (0.27, 29.2) 1 incidence study CLL Quantitative & qualitative exposure assessment: mRR=1.14 (0.78, 1.67) 18 studies Quantitative to some industrial hygiene sampling: mRR=1.38 (0.71, 2.69) 8 studies Quantitative or semi-quantitative estimates: mRR=1.54 (0.72, 3.31) 7 studies Quantitative exposure assessment: mRR=2.44 (0.88, 6.75) 4 studies (1 incidence, 3 mortality)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure[**] (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Vlaanderen 2012 **Meta-analysis**	Benzene	76 76 29 29 18	CML Quantitative & qualitative exposure assessment: mRR=1.23 (0.93, 1.63) 17 studies Quantitative to some industrial hygiene sampling: mRR=1.44 (0.82, 2.53) 6 studies Quantitative or semi-quantitative estimates: mRR=1.44 (0.82, 2.53) 6 studies Quantitative exposure assessment: mRR=1.68 (0.74, 3.84) 3 studies (2 incidence, 1 mortality)		
Cohort studies					
Anttila 1995[€] Incidence 3,089 TCE workers 1967-1992	TCE (urine TCA)				Urine TCA (μmol/L) # cases <100: SIR=0.39 (0.01, 2.19) 1 ≥100: SIR=2.65 (0.72, 6.78) 4
Radican 2008[€] Mortality 14,455 1953-2000	Aircraft maintenance TCE (JEM)			Cumulative exposure (unit-yrs) Men (HR) # cases >0-5: 0.9 (0.4, 2.0) 11 >5-25: 0.5 (0.2, 1.6) 4 >25: 0.9 (0.4, 2.1) 9 Women (HR) # cases >0-5: 0.4 (0.1, 2.7) 1 >5-25: — 0 >25: 0.5 (0.1, 2.2) 2	Men HR # cases Low, intermittent: 1.0 (0.4, 2.7) 13 Low, continuous: 1.2 (0.4, 3.4) 10 Peak, infrequent: 1.8 (0.5, 5.8) 5 Peak, frequent: 1.3 (0.5, 3.6) 10
Balu 2011[€] Mortality 5,016 white males 1953-2003	TCE (Qualitative JEM)	20 5 15	Exposure Level 2: SRR=0.73 (0.15, 3.45) 3: SRR=1.89 (0.61, 5.86)		
Hansen 2013 Incidence 5,553 Finland:1967-2004 Sweden: 1958-2003 Denmark: 1968-2008	TCE (Urine TCA was used to identify workers ever exposed to TCE)	23 19 4	SIR=1.06 (0.67, 1.60) SIR=1.19 (0.72, 1.86) males SIR=0.70 (0.19, 1.79) females	—	—
Saberi Hosnijeh 2013 Incidence 241,465 1992-2010	TCE (JEM) Benzene (JEM)		Myeloid leukemia (179 cases) (RR) # cases Low: 1.02 (0.74, 1.39) 70 High: 0.60 (0.24, 1.51) 5 Low: 1.15 (0.78, 1.70) 39 High: 1.60 (0.95, 2.69) 17	Lymphoid leukemia (225 cases) # cases 0.91 (0.68, 1.20) 85 0.76 (0.37, 1.59) 8 1.06 (0.75, 1.50) 51 0.52 (0.25, 1.06) 8	

Reference, type of cancer data, total # of subjects, follow-up period	Exposure** (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Silver 2014 Mortality (Non-CLL Cases=77) 34,494 1969-2009	Microelectronics plant TCE (JEM) PCE (JEM)		5 exposure-yrs cumulative exposure: HR=1.31 (0.98, 1.75) HR=1.05 (0.66, 1.66)	—	—
Case-Control Studies					
Seidler 2007[¶] Incidence 104 cases of CLL 710 controls	TCE Benzene	18 24			Cumulative exposure (ppm*yr) # cases >0-≤8.6: OR=1.1 (0.5, 2.4) 10 >8.6-≤130: OR=0.7 (0.3, 1.7) 6 >130: OR=0.9 (0.2, 4.5) 2 >0-≤8.6: OR=0.8 (0.4, 1.8) 8 >8.6-≤130: OR=1.6 (0.8, 3.2) 14 >130: OR=0.7 (0.1, 3.1) 2
Costantini 2008[β] Incidence 586 Leukemias 1,278 controls 1991-1993	TCE PCE Benzene		Exposure intensity (OR) # cases Leukemias AML CLL TCE Very low/Low: 1.0 (0.5, 1.8) 17 1.0 (0.4, 2.5) 6 1.2 (0.5, 2.7) 8 Medium/High: 0.7 (0.4, 1.5) 11 1.1 (0.5, 2.9) 6 0.9 (0.3, 2.6) 4 PCE Very low/Low: 0.6 (0.2, 1.6) 6 -- 2 --- 3 Medium/High: 1.0 (0.4, 2.7) 7 -- 2 --- 1 Benzene Very low/Low: 0.5 (0.3, 0.9) 16 0.3 (0.1, 1.0) 3 0.7 (0.3, 1.4) 11 Medium/High: 1.3 (0.7, 2.3) 25 0.9 (0.4, 2.3) 6 1.8 (0.9, 3.9) 12		Years of Exposure (OR) # cases CLL <15: 0.7 (0.1, 3.4) 2 >15: 1.2 (0.2, 6.2) 2 ≤15: 1.8 (0.7, 4.6) 9 >15: 4.7 (0.8, 26) 3
Cocco 2013 Incidence 689 CLL cases 4,279 controls 1991-2004	TCE (questionnaires, workplace inspections)	70 23 36 11	Probability of Exposure (OR): Low: 1.1 (0.7, 1.8) Medium: 0.9 (0.6, 1.2) High: 2.0 (1.0, 4.0)	High exp. prob./Duration # cases 1-14 years: OR=0.9 (0.3, 3.2) 3 15-29 years: OR=2.3 (0.6, 8.7) 3 30-39 years: OR=3.8 (1.0, 14) 4 40+ years: OR=4.3 (0.3, 69) 1	High exp. prob./Intensity level (ppm) ≤5: OR=1.4 (0.3, 7.0) 2 cases 5-75: OR=1.7 (0.7, 4.0) 7 cases >75: OR=3.2 (0.6, 18) 2 cases

Reference, type of cancer data, total # of subjects, follow-up period	Exposure[^^] (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Talibov 2014[#] Incidence 15,332 AML cases 76,660 controls 1961-2005	(JEM) TCE PCE Benzene	 645 172 808	Cumulative exposure percent: TCE (RR) (# cases) total # Males # Females # <50th: 0.9 (0.8, 1.1) 302 0.9 (0.8, 1.1) 239 1.2 (0.7, 1.9) 63 50-90th: 1.1 (0.9, 1.3) 275 1.1 (0.9, 1.3) 225 1.4 (0.9, 2.4) 50 >90th: 1.1 (0.8, 1.5) 68 1.1 (0.8, 1.5) 49 1.5 (0.7, 3.3) 19 PCE total # <50th: 1.1 (0.8, 1.4) 89 50-90th: 0.8 (0.6, 1.1) 67 >90th: 0.7 (0.4, 1.3) 16	Benzene (RR) (# cases) total Males # Females # 1.0 (0.8, 1.2) 430 1.1 (0.9, 1.4) 350 0.9 (0.6, 1.2) 81 0.9 (0.7, 1.1) 310 0.9 (0.7, 1.2) 264 1.1 (0.7, 1.7) 45 0.8 (0.6, 1.2) 68 0.8 (0.5, 1.1) 63 2.0 (0.6, 7.0) 5	
Dry Cleaning Studies					
Blair 2003 Mortality 5,369 1948-1993	Dry cleaning	12	Any exposure: SMR=0.8 (0.4, 1.4)	—	—
Selden 2011 Incidence 9,440 1985-2006	Dry Cleaning & Laundry Workers (plant survey, work history)	11 11	Lymphoid leukemia: SIR=1.01 (0.51, 1.81) Myeloid leukemia: SIR=1.06 (0.53, 1.89)		
Morton 2014 Incidence 2,440 CLL/SLL cases 152 ALL cases 23,096 controls	Dry cleaning		Any exposure: CLL/SLL: OR=1.20 (0.66, 2.18) ALL: OR=1.10 (0.15, 8.12)	—	—
't Mannetje 2015 Incidence 1,014 CLL/SLL cases 12,025 controls	Dry cleaning		Not employed as dry cleaner is referent: OR=1.21 (0.67, 2.21)	—	—
Benzene Workers Studies					
Orsi 2010 Incidence 2000-2004 77 CLL cases 305 controls	Benzene (JEM)	21 18	Any exposure: OR=0.6 (0.3, 1.0) Benzene >1ppm: OR=0.6 (0.3, 1.1)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure** (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Schnatter 2012 Incidence & Mortality 60 AML cases & 241 controls 28 CML cases & 122 controls 80 CLL cases & 345 controls 1950-2006	Benzene (work histories, plant monitoring data)		Average Exposure (ppm) AML # cases .016-.081: OR=2.0 (0.9, 4.5) 15 .081-.259: OR=1.4 (0.6, 3.3) 13 >.259: OR=1.9 (0.9, 4.2) 16 CLL .016-.081: OR=0.7 (0.4, 1.5) 15 .081-.259: OR=0.8 (0.4, 1.6) 19 >.259: OR=0.8 (0.4, 1.7) 15 CML .016-.081: OR=1.8 (0.6, 5.0) 9 .081-.259: OR=2.2 (0.7, 6.9) 8 >.259: OR=0.9 (0.3, 3.3) 4	Duration of employment (yrs) # cases AML 15.6-28: OR=1.0 (0.5, 2.0) 16 >28: OR=1.7 (0.8, 3.9) 17 CLL 15.6-28: OR=2.1 (1.1, 4.2) 36 >28: OR=1.2 (0.6, 2.6) 26 CML 15.6-28: OR=3.1 (0.9, 10.6) 14 >28: OR=1.4 (0.4, 5.7) 8	Cumulative exposure (tertiles, ppm-yrs) AML # cases 0.348-2.93: OR=1.04 (0.50, 2.19) 19 >2.93: OR=1.39 (0.68, 2.85) 21 CLL 0.348-2.93: OR=1.49 (0.81, 2.76) 32 >2.93: OR=1.05 (0.56, 1.98) 24 CML 0.348-2.93: OR=5.04 (1.45, 17.5) 16 >2.93: OR=2.20 (0.63, 7.68) 8
Linet 2015 Incidence 73,789 exposed 35,504 unexposed 1972-1999	Benzene Exposed vs unexposed	61 8 13 26 2	Leukemias: RR = 2.8 (1.6, 5.5) ALL: RR = 4.5 (0.8, 83.9) CML: RR = 2.5 (0.8, 10.7) AML: RR = 2.1 (0.9, 5.2) CLL: RR = no cases unexposed	—	—
Steneljem 2015 Incidence 24,917 1999-2011	Benzene (offshore oil industry workers) (JEM)	8 11	Any exposure: AML: RR = 2.18 (0.47, 10) CLL: RR = 5.40 (0.70, 41)	Years exposed (RR) # cases AML CLL >0-5.49: 2.0 (0.3, 13) 3 7.6 (0.9, 63) 5 5.5-<13: 3.4 (0.7, 17) 4 4.8 (0.5, 47) 3 ≥ 13: 1.0 (0.1, 11) 1 4.0 (0.4, 39) 3	Cumulative exposure (tertiles) (RR) AML # cases CLL # cases 1: 1.4 (0.2, 11) 2 6.2 (0.7, 54) 4 2: 0.9 (0.1, 9.3) 1 3.1 (0.3, 34) 2 3: 4.9 (0.9, 27) 5 6.7 (0.8, 60) 5 Average exposure (tertiles) (RR) AML # cases CLL # cases 1: 0.8 (0.1, 8.7) 1 2.9 (0.3, 31) 2 2: 2.5 (0.4, 15) 3 7.6 (0.9, 65) 5 3: 3.5 (0.6, 19) 4 5.9 (0.6, 56) 4
Vinyl Chloride Workers Study					
Hsieh 2011 Mortality 3,336 1980-2007	Polyvinyl chloride workers	8 6	SMR=2.62 (1.13, 5.16) SMR=3.93 (1.40, 8.54) during high exposure period (1980-1997)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure** (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Drinking Water Studies					
Aschengrau 1993 Incidence 34 cases 737 controls 1983-1986	PCE levels in drinking water (modeling)	 5 2 3	Exposure (OR) Any: 1.72 (0.50, 4.71) Low: 0.84 (0.09, 3.48) High: 5.78 (0.98, 23) High: adj OR=5.84 (1.37, 24.91)	—	—
Cohn 1994 Incidence 75 towns in NJ 1979-1987 663 cases, male 527 cases, female	Municipal Drinking water (sample data) TCE	M F 663 527 162 156 63 56 64 54 16 22 3 7 205 149 55 40 25 18 155 121 37 40 15 7 76 70 15 16 6 10	Males 0.1-5 ppb: RR=0.85 (0.71, 1.02) >5 ppb: RR=1.10 (0.84, 1.43) 0.1-5 ppb: RR=0.91 (0.53, 1.57) >5 ppb: RR=0.54 (0.17, 1.70) 0.1-5 ppb: RR=1.01 (0.74, 1.39) >5 ppb: RR=1.49 (0.97, 2.30) 0.1-5 ppb: RR=0.83 (0.58, 1.21) >5 ppb: RR=1.08 (0.63, 1.86) 0.1-5 ppb: RR=0.63 (0.36, 1.11) >5 ppb: RR=0.82 (0.35, 1.91)	Total leukemias Acute lymphocytic leukemia Chronic lymphocytic leukemia Acute myelogenous leukemia Chronic myelogenous leukemia	Females RR=1.13 (0.93, 1.37) RR=1.43 (1.07, 1.90) RR=1.85 (1.03, 3.70) RR=2.36 (1.03, 5.45) RR=0.99 (0.68, 1.44) RR=1.57 (0.95, 2.60) RR=1.23 (0.84, 1.81) RR=0.75 (0.35, 1.63) RR=0.83 (0.47, 1.48) RR=1.79 (0.90, 3.55)
	PCE	663 527 150 127 80 83 64 54 10 21 8 9 205 149 48 37 28 19	0.1-5 ppb: RR=0.90 (0.75, 1.08) >5 ppb: RR=0.84 (0.66, 1.06) 0.1-5 ppb: RR=0.55 (0.27, 1.12) >5 ppb: RR=0.81 (0.38, 1.72) 0.1-5 ppb: RR=0.94 (0.68, 1.32) >5 ppb: RR=0.98 (0.65, 1.47)	Total leukemias Acute lymphocytic leukemia Chronic lymphocytic leukemia	RR=1.05 (0.85, 1.29) RR=1.20 (0.94, 1.52) RR=1.89 (1.04, 3.44) RR=1.58 (0.74, 3.36) RR=1.01 (0.69, 1.48) RR=0.93 (0.56, 1.52)

Reference, type of cancer data, total # of subjects, follow-up period	Exposure** (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Bove 2014a (Camp Lejeune Marines/Navy) Mortality 154,932: Camp Lejeune 154,969: Camp Pendleton 1979-2008	VOC contaminated drinking water (modeled) vs U.S. population vs. Camp Pendleton	66	SMR=0.78 (0.60, 0.99) HR = 1.11 (0.75, 1.62)	Any exposure (months): 1-3: OR=1.8 (0.8, 3.9) 9 cases 4-6: OR=1.7 (0.7, 4.3) 6 cases 7-12: OR=0.9 (0.4, 2.2) 6 cases >12: OR=0.9 (0.5, 1.6) 22 cases	TCE Cumulative exposure (HR) Low: 2.0 (1.0, 4.0) 16 cases Medium: 1.5 (0.7, 3.4) 11 cases High: 1.8 (0.9, 3.9) 13 cases
Bove 2014b (Camp Lejeune Civilian workers) Mortality 4,647: Camp Lejeune 4,690: Camp Pendleton 1979-2008	VOC contaminated drinking water (modeled) vs U.S. population vs. Camp Pendleton	12	SMR = 1.55 (0.80, 2.71) HR = 1.59 (0.66, 3.84)	—	Cumulative exposure (HR) TCE Medium: 1.0 (0.1, 7.4) 2 cases High: 1.8 (0.4, 9.3) 8 cases PCE Medium: 0.9 (0.1, 7.0) 2 cases High: 1.7 (0.3, 8.5) 8 cases

* The results are for all leukemias combined unless otherwise noted.

** Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.

*** One study was included that did not report the number of leukemia cases and whether the cases were incident or deaths.

**** One study did not report the number of leukemia cases.

€ Included in the Karami et al. 2013 meta-analysis.

¶ Included in the Cocco 2013 study but provided additional information on benzene as well as results for cumulative exposure to TCE.

β Included in the Khalade et al. 2010 meta-analysis of benzene and leukemias.

The Talibov et al. 2014 study did not present separate results by gender for PCE cumulative exposure.

JEM: job-exposure matrix

Chronic lymphocytic leukemia/small lymphocytic leukemia **(CLL/SLL)**

ALL: Acute lymphocytic leukemia

CLL: Chronic lymphocytic leukemia

AML: Acute myelogenous leukemia

CML: Chronic myelogenous leukemia

RR: Risk Ratio
OR: Odds Ratio
SMR: Standardized Mortality Ratio
SIR: Standardized Incidence Ratio
95% CI: 95% Confidence Interval
sRR: Summary Risk Ratio
mRR: Meta-analysis summary risk ratio.
HR: Hazard Ratio
JEM: Job-exposure matrix
I: Incidence; M: mortality
VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)
Urine TCA: urine levels of trichloroacetic acid, a metabolite of TCE.

Summary of IARC's review of benzene and leukemias

IARC review of benzene (IARC 2012): "Benzene causes acute myeloid leukaemia/acute non-lymphocytic leukaemia. Also, a positive association has been observed between exposure to benzene and acute lymphocytic leukaemia, chronic lymphocytic leukaemia, multiple myeloma, and non-Hodgkin lymphoma."

ATSDR Assessment

In the assessment of the evidence for causation, ATSDR placed high weight on assessments conducted by EPA, NTP and IARC as well as the meta-analyses. High weight was also given to a study that evaluated leukemia types, pooled data from other studies, or provided mechanistic information. Our assessment of the epidemiological evidence considered some of the viewpoints associated with Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if $\leq$1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding.

TCE:

The meta-analyses (Alexander et al. 2006, Karami et al. 2013) are in agreement with a summary RR for leukemias from TCE exposure of about 1.10. A case-control study primarily focused on benzene exposure also evaluated TCE but was not included in the meta-analyses (Costantini et al. 2008). In this study TCE exposures were likely low even among those classified as having "medium/high" exposure intensity. Among those classified as having "medium/high" exposure, no elevation was observed for all leukemias or CLL, and an OR near the null was observed for AML.

Subsequent to the Karami et al. 2013 meta-analysis, three cohort studies and two case-control studies have been published. Two cohort studies found elevated risks in the range of 1.2 and 1.3 (Hansen et al. 2013, Silver et al. 2014), although one of these studies found the elevation only among male workers (Hansen et al. 2013). The Silver et al. 2014 focused on mortality from non-CLL leukemias that likely were predominantly myeloid leukemias. No elevation was observed in the Saberi Hosnijeh et al. 2013 cohort study although there were small numbers of cases in the high exposure group, a generic JEM was used which likely introduced considerable non-differential exposure misclassification, and there was limited information on duration of employment, work history and exposure to particular chemicals. A pooled case-control study observed exposure-response trends for exposure duration and exposure intensity among workers with high probability of TCE exposure and CLL, although the analyses were based on small numbers of exposed cases (Cocco et al. 2013). A case-control study of AML observed RRs for cumulative exposure near the null for males, and a monotonic trend for females with a RR of 1.5 (95% CI: 0.7, 3.3) at the >90th percentile of cumulative exposure (Talibov et al. 2014). The study was limited by an exposure assessment that relied on census data for occupation and a generic JEM which likely introduced considerable exposure misclassification.

The New Jersey drinking water study (Cohn et al. 1994) observed elevated risks for CLL in both sexes, and elevated risks in females only for ALL and CML. For ALL, the elevated risk in females was virtually all due to childhood ALL. The RR for AML in males was 1.08 and was not elevated in females. The Camp Lejeune mortality study of Marines and Navy personnel (Bove et al. 2014a) observed elevated risks among those exposed for shorter durations (1-6 months) but not for longer durations (>6 months). Elevated risks were observed among those with any cumulative exposure compared to unexposed, but the exposure-response trend was not monotonic. The Camp Lejeune mortality study of civilian workers (Bove et al. 2014b) observed a monotonic exposure-response trend for cumulative exposure based on small numbers of exposed cases.

The above table lists studies that evaluated adult leukemias. However, although childhood leukemia was not a focus of this assessment, for completeness, ATSDR notes the existence of two drinking water case-control studies that evaluated TCE and childhood leukemia. In the Woburn MA study, TCE was the primary contaminant in the drinking water with measured levels as high as 267 ppb. Residential exposure to the contaminated drinking water during pregnancy resulted in an odds ratio of 8.3 (95% CI: 0.7, 95) for ALL which increased to 14.3 (95% CI: 0.9, 225) for those exposed to >50th percentile cumulative exposure (Costas et al. 2002). In the Camp Lejeune study, residential TCE drinking water exposure was not associated with the combined outcome, childhood leukemia and childhood NHL (Ruckart et al. 2013).

Animal and mechanistic information

Evidence from animal data indicates that TCE causes autoimmune disorders (EPA 2011). In humans, TCE has been associated with systemic sclerosis (EPA 2011). In a pooled analysis, systemic sclerosis was associated with leukemia based on 2 studies: SIR=2.75 (95% CI: 1.32, 5.73) (Onishi et al. 2013). In general, there is human and animal evidence that TCE is associated with immunomodulation, autoimmunity and immune suppression, and that these immune disorders are associated with hematopoietic cancers such as leukemias (EPA 2011, NTP 2015). In a study of factory workers in China exposed to TCE, declines in lymphoid cell types including B cells and $CD4^+$ T cells were observed (Bassig et al. 2016). This finding supports an association between TCE and the lymphoid leukemias, ALL and CLL. There is strong evidence that autoimmune disorders are associated with myeloid leukemias and myelodysplastic syndromes as well as lymphoid leukemias (Anderson et al 2009, Kristinsson et al 2011, Gunnarsson et al 2016).

Conclusion: ATSDR concludes that the epidemiological evidence for TCE and leukemia from the occupational and drinking water studies is not strong but nevertheless sufficient to at least reach equipoise. The meta-analyses indicated a risk of about 1.10. Although not consistent, positive findings in human studies have been observed for each leukemia type. The strongest findings were for CLL (Cocco et al. 2013). But elevated risks have also been observed for AML (Constantini et al. 2008, Talibov et al. 2014), ALL (Cohn et al. 1994) and CML (Cohn et al. 1994). In addition, the Silver et al 2014 study observed an elevated risk for non-CLL leukemias which likely were predominantly myeloid leukemias. Supporting evidence comes from human and animal studies indicating that TCE causes immune disorders that have been linked to leukemias. Moreover, a study of TCE exposure among factory workers in China observed declines in lymphoid cell types, supporting an association with lymphoid leukemias (Bassig et al. 2016).

Based on the epidemiological evidence, the link between TCE-associated immune disorders and leukemias, including myeloid as well as lymphoid leukemias, and the evidence that TCE affects lymphoid cell types, ATSDR concludes that there is **equipoise and above evidence for causation for TCE and all adult leukemias, including AML, ALL, CML and CLL.**

PCE:

No meta-analyses have been conducted for PCE and leukemias. A large cohort mortality study of dry cleaning workers did not observe an elevated risk (Blair et al. 2003). A second cohort study combined dry cleaning workers with laundry workers that were unlikely to be exposed to PCE and obtained SIRs near the null (Selden et al. 2011). Two case-control studies of dry cleaning workers observed elevated risks for CLL/SLL of about 1.2 (Morton et al. 2014, t'Mannetje et al. 2015). The Morton et al. 2014 study obtained an OR of 1.10 (95% CI: 0.15, 8.12) for ALL. A cohort mortality study observed a risk near the null for all leukemia (Silver et al. 2014). A case-control study observed no elevation in risk for all leukemias (Costantini et al. 2008), and a case-control study of AML observed an RR near the null for low cumulative exposure and no elevation at higher levels of exposure (Talibov et al. 2014). PCE-contaminated drinking water and leukemia was evaluated in the Cape Cod study (Aschengrau et al. 1993). Any PCE exposure was associated with an elevated risk of 1.7 which increased to 5.8 for those exposed above the 90th percentile. In the NJ drinking water study, elevated risks for ALL was observed only among females (Cohn et al. 1994).

Animal information: Inhalation exposure to PCE was associated with mononuclear-cell leukemia in rats of both sexes. EPA concluded that there was sufficient evidence for a causal association between PCE and mononuclear-cell leukemia in rats (EPA 2012). However, the relevance of this association to humans continues to be debated. Large granular lymphocyte (LGL) cells exist in humans that are similar to the cells involved in mononuclear-cell leukemia in the rat. Disorders associated with LGL cells include lymphoproliferative disorders such as NHL, Hodgkin lymphoma, multiple myeloma, hairy cell leukemia, and B-cell lymphoproliferative disorders as well as autoimmune diseases such as lupus (EPA 2012).

Conclusion: Because of the limited number of epidemiological studies, the mixed results in the studies of dry cleaning workers who most likely have the highest exposures to PCE, and the uncertainties regarding the relevance of the finding of mononuclear-cell leukemia in the rat, ATSDR concludes that there is **below equipoise evidence for causation for PCE and leukemias**.

Benzene:

AML is known to be caused by benzene exposure (IARC 2012). IARC (IARC 2012) has concluded that positive associations exist for ALL and CLL. The epidemiological evidence from the meta-analyses (Khalade 2010, Vlaanderen 2011, 2012) indicates that benzene causes all types of leukemia. The Vlaanderen meta-analysis was not available for IARC's review of benzene. This meta-analysis observed no publication bias and, with the exception of CLL, no evidence of between-study heterogeneity when the analyses were restricted to studies with quantitative exposure assessments. The meta-analysis found elevated risks for benzene exposure and all 4 types of leukemia (Vlaanderen et al. 2011, 2012). In the meta-analysis conducted by Khalade et al. 2010, monotonic exposure-response trends were observed for cumulative exposure to benzene and all leukemia combined and AML. The exposure-response trend for

CLL was not monotonic but indicated an increased risk at the highest cumulative exposure level (Khalade et al. 2010). A case-control study not included in the meta-analyses evaluated CLL and used a generic JEM to assign exposures (Orsi et al. 2010). The authors stated that exposures to benzene were very low, and no elevation of risk was observed.

Four cohort studies have been conducted since the publication of the Vlaanderen et al. 2011, 2012 meta-analyses. Saberi Hosnijeh et al. 2013 found an elevated risk for myeloid leukemia but not for lymphoid leukemia. Schnatter et al. 2012 observed an increased risk of AML with increasing cumulative exposure to benzene. CML risks were higher in the lower exposure groups than in the high exposure group and no clear pattern was observed for CLL. The Linet et al. 2015 study found elevated risks for ALL, CML and AML but could not evaluate CLL because there were no unexposed cases. Stenehjem et al. 2015 observed elevated risks for AML and CLL but the exposure-response trends were not monotonic.

In a study of factory workers in China exposed to benzene, declines were seen in both myeloid and lymphoid cell types (Bassig et al. 2016). These findings provide supporting evidence for associations between benzene and all types of leukemia, myeloid and lymphoid.

Conclusion: Based on the results of the meta-analyses, the recent cohort studies and the finding that occupational benzene exposure is associated with reductions in both lymphoid and myeloid cell types, ATSDR concludes that there is **sufficient evidence for causation for benzene and all leukemia types, i.e., ALL, CLL, AML, and CML**.

Vinyl Chloride: A meta-analysis observed no elevation in risk (Boffetta 2003). However a study of polyvinyl chloride workers observed excess mortality, especially during the period of high exposures (SMR=3.93, 95% CI: 1.40, 8.54) (Hsieh 2011). Because of the conflicting findings between the latter study and the meta-analysis, ATSDR concludes that there is **below equipoise evidence for causation for vinyl chloride and leukemias**.

Liver Cancer

Reference, type of cancer data, total # of subjects, follow-up period	Exposure[c] (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Boffetta 2003 **Meta-analysis**	Vinyl chloride	188 101	SMR=2.96 (2.00, 4.39) 6 studies SMR=1.35 (1.04, 1.77) for liver cancers **except angiosarcoma** 4 studies		
Alexander 2007 **Meta-analysis**	TCE-exposed sub-cohorts	49	sRR = 1.41 (1.06, 1.87) for primary liver disease (5 studies, 4 I, 1 M)		—
Scott 2011 **EPA Meta-analysis**	TCE: All studies High exposure group	102 (?)[**]	sRR = 1.29 (1.07, 1.56) 9 studies (8 cohort studies - 4 incidence, 4 mortality; 1 case-control – mortality) sRR = 1.28 (0.93, 1.77) 8 cohort studies		
Cohort Studies					
Anttila 1995[d] Incidence 3,089 TCE workers 1967-1992	TCE (urine TCA)				Urine TCA (µmol/L) # cases <100: SIR=1.64 (0.20, 5.92) 2 ≥100: SIR=2.74 (0.33, 9.88) 2
Raaschou-Nielsen 2003[f] Incidence 40,049 1964-1997	TCE (job title, plant air monitoring & urine TCA data)	27 7	Any exposure (SIR): Men: 1.1 (0.7, 1.6) Women: 2.8 (1.1, 5.8)	Duration of employment (years), # cases: <1: men, RR=1.3 (0.6, 2.5) 9 women, RR=2.8 (0.3, 10.0) 2 1-4.9: men, RR=1.0 (0.5, 1.9) 9 women, RR=4.1 (1.1, 10.5) 4 ≥5: men, RR=1.1 (0.5, 2.1) 9 women, RR=1.3 (0.0, 7.1) 1	
Radican 2008[e] Mortality 10,730 male workers 1953-2000 **NTP: Moderate Utility**	TCE (men only) Aircraft maintenance (JEM)	8	Any TCE exposure: HR=2.72 (0.34, 21.88)	Cumulative exposure score (unit-yrs): 0-5: HR=3.28 (0.37, 29.5) 4 cases 5-25: HR=0 >25: HR=4.05 (0.45, 36.4) 4 cases	Exposure intensity HR # cases Low, intermittent: 3.8 (0.5, 30) 8 Low, continuous: 1.3 (0.1, 14) 2 Peak, infrequent: 6.4 (0.7, 62) 3 Peak, frequent: 2.1 (0.2, 20) 3
Lipworth 2011 Mortality 5,443 TCE workers 5,830 PCE workers 1960-2008	Aircraft manufacturing TCE (JEM) PCE (JEM)	 24 19	Any exposure: SMR=0.89 (0.57, 1.33) SMR=0.93 (0.56, 1.45)	Years exposed (RRs): TCE <1: 0.67 (0.32, 1.42) 10 cases 1-4: 0.69 (0.28, 1.71) 6 cases >4: 0.83 (0.36, 1.91) 8 cases PCE <1: 0.71 (0.25, 2.02) 4 cases 1-4: 0.93 (0.38, 2.27) 6 cases >4: 1.29 (0.60, 2.78) 10 cases	—
Bahr 2011 Mortality 5,016 white males 1953-2003	TCE (Qualitative JEM)	Not reported	Exposure Level 2: SRR=0.34 (0.05, 2.07) 3: SRR=0.39 (0.08, 1.94)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Hansen 2013 Incidence 5,553 Finland:1967-2004 Sweden: 1958-2003 Denmark: 1968-2008 **NTP: Moderate Utility**	TCE (urine TCA)	36 21	Liver & biliary passages: SIR=1.77 (1.24, 2.45) Liver, primary: SIR=1.93 (1.19, 2.95)	Liver & biliary passages, 20 yr. lag: SIR=2.09 (1.34, 3.11) 24 cases	Liver & biliary passages: Urine TCA (mg/L) (RR) # cases 5-25: 0.66 (0.31, 1.42) 12 25-50: 0.45 (0.13, 1.54) 5 >50: 0.63 (0.22, 1.68) 3
Silver 2014 Mortality 34,494 1969-2009	Microelectronics plant TCE (JEM) PCE (JEM)	39[¶]	5 exposure-yrs cumulative exposure: HR=0.99 (0.50, 1.95) HR=0.79 (0.27, 2.30)		
Case-Control Study					
Christensen 2013 Incidence 48 cases 1,834 controls 1979-1985	TCE PCE	1 1 1 1	"any"exposure: OR=1.1 (0.1, 11) "substantial": OR= 2.5 (0.3, 25) "any"exposure: OR=3.3 (0.2, 60) "substantial": OR=4.4 (0.2, 103)	–	–
Vlaanderen 2013 Incidence 23,896 cases 119,480 controls 1961-2005	TCE (JEM) PCE (JEM)		Cumulative exposure tertiles, HR, # cases TCE # cases PCE # cases Benzene # cases 1: 1.03 (0.91, 1.16) 340 0.91 (0.73, 1.14) 90 1.00 (0.89, 1.12) 373 2: 0.99 (0.90, 1.09) 508 1.18 (0.97, 1.44) 121 1.04 (0.94, 1.15) 497 3: 1.00 (0.90, 1.11) 422 1.13 (0.92, 1.38) 114 1.14 (1.03, 1.26) 485		>90th percentile cumulative exposure: TCE: HR=1.02 (0.82, 1.25) 106 cases PCE: HR=1.11 (0.79, 1.57) 40 cases >90th percentile, intensity x freq. TCE: HR=1.08 (0.90, 1.30) 137 cases PCE: HR=1.26 (0.88, 1.80) 38 cases
Dry Cleaning Workers Studies					
Blair 2003 Mortality 5,369 1948-1993	Dry Cleaning	10	Any exposure: SMR=0.8 (0.4, 1.5)		
Lynge 2006 Incidence 69 cases 493 controls 1970-2001	Dry Cleaning	11	Unexposed as referent: RR=0.76 ((0.38, 1.52)		
Selden 2011 Incidence 6,356 1985-2006	Dry Cleaning: PCE sub-cohort (plant survey, work history)	8[¶] 10[¶]	Any exposure: Men: SIR=2.14 (0.92, 4.21) Women: SIR=0.90 (0.43, 1.65)	Duration of employment (SIR) # cases <1 year 1-4 years >4 years Men: 0.0 3.2 (0.7, 9.3) 3 2.1 (0.7, 4.8) 5 Women 1.7 (0.2, 6.0) 2 1.5 (0.5, 3.5) 5 0.5 (0.1, 1.3) 3	

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Vinyl Chloride Workers Studies					
Marsh 2007	Vinyl chloride (historical modeling based on analysis of chemical processes and validated by air monitoring data)	2		Duration (yrs) RR SMR # cases 0: — 1.1 (0.6, 1.8) 15 >0-5: 2.5 (0.4, ∞) 0.4 (0.0, 2.1) 1 5-9: 0.7 (0.0, ∞) 2.4 (0.1, 13) 1 10+: — — 0	Cumulative exposure (tertiles) RR SMR # cases Unexposed: — 1.1 (0.6, 1.8) 15 1: — — 0 2: 1.0 (0.0, 6.7) 0.9 (0.0, 4.8) 1 3: 0.4 (0.0, 2.6) 0.4 (0.0, 2.0) 1
Gennaro 2008 Mortality 812 Autoclave, PVC baggers & PVC compound workers 1972-1999	Vinyl chloride	7 1 5	Autoclave workers: RR=9.57 (3.71, 24.7) PVC baggers: RR=0.82 (0.23, 2.93) PVC compound workers: RR=2.46 (0.94, 6.42)		
Hsieh 2011 Mortality 3,336 1980-2007	Polyvinyl chloride workers	56 33	SMR=1.32 (1.00, 1.72) SMR=1.93 (1.37, 2.79) during high exposure period		
Carreón 2014 Mortality 1,874 1960-2007	Vinyl chloride	11[Y] 11[Y]	Any exposure: SMR=3.80 (1.89, 6.80) Exposed <1975: SMR=4.20 (2.09, 7.51)	Duration of vinyl chloride exposure: <7.4 years: SMR=1.26 (0.26, 3.69) 3 cases 7.4 - <16 years: SMR=3.94 (0.48, 14.2) 2 cases ≥16 years: SMR=10.9 (4.01, 23.8) 6 cases	
Benzene Workers Study					
Linet 2015 Incidence 73,789 exposed 35,504 unexposed 1972-1999	Benzene	286	RR=1.2 (0.9, 1.4)		
Drinking Water Studies					
Bove 2014a (Camp Lejeune Marines/Navy) Mortality 154,932: Camp Lejeune 154,969: Camp Pendleton 1979-2008	VOC-contaminated drinking water (modeled) vs. U.S. population vs. Camp Pendleton	51[Y]	SMR=0.74 (0.55, 0.97) HR=1.42 (0.92, 2.20)	Any residential exposure # cases: 1-3 months, OR=1.3 (0.5, 3.5) 5 4-6 months, OR=1.5 (0.5, 4.4) 4 7-12 months, OR=1.2 (0.5, 2.9) 6 >12 months, OR=1.0 (0.5, 1.8) 18	Modeled residential cumulative exposure to TCE: (no exposure as referent) "very low": HR=1.30 (0.74, 2.29) "medium/high": HR=1.34)0.84, 2.16)

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Bove 2014b (Camp Lejeune Civilian Workers) Mortality 4,647: Camp Lejeune 4,690: Camp Pendleton 1979-2008	VOC-contaminated drinking water (modeled) vs. U.S. population vs. Camp Pendleton	3[Ψ]	SMR=0.42 (0.09, 1.21) HR=0.62 (0.16, 2.45)		

* Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.

** One study included in the meta-analysis did not report the number of exposed cases.

£ Included in the EPA (Scott and Jinot 2011) and Alexander et al. 2007 meta-analyses. Included in the table because of information on exposure-response relationships (urine-TCA levels, duration of employment).

€ Included in the EPA meta-analyses. Included in the table because of information on exposure intensity and cumulative exposures for men only. (There were no exposed primary liver cancer cases among women.)

Ψ Liver/biliary/gall bladder cancers.

RR: Risk Ratio

OR: Odds Ratio

SMR: Standardized Mortality Ratio

SIR: Standardized Incidence Ratio

95% CI: 95% Confidence Interval

sRR: Summary Risk Ratio

HR: Hazard Ratio

JEM: Job-exposure matrix

I: Incidence; M: mortality

VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)

Urine TCA: urine levels of trichloroacetic acid, a metabolite of TCE.

Summary of NTP, EPA, and IARC reviews of TCE and vinyl chloride and liver cancer:

NTP Monograph on TCE (NTP 2015): "The epidemiological data suggest that trichloroethylene may be associated with a modest increase in the risk of liver cancer, based primarily on the two meta-analyses. However, the findings are inconsistent across studies, and there was little evidence for exposure-response relationships in the individual studies or the meta-analyses. In addition, the role of chance or confounding by one or more common occupational co-exposures or lifestyle factors cannot be completely ruled out."

EPA Toxicological Review of TCE (EPA 2011): "The evidence is more limited for liver cancer mainly because only cohort studies are available and most of these studies have small numbers of cases."

IARC review of TCE (IARC 2014) concluded that a positive association was observed between TCE exposure and liver cancer. However, IARC also noted: "Although some positive associations were observed in cohort studies, the results were somewhat inconsistent."

IARC review of vinyl chloride (IARC monograph 100F, 2012) concluded: "There is compelling evidence that exposure to vinyl chloride is associated with angiosarcoma of the liver, and strong evidence that it is associated with hepatocellular carcinoma. Together with the observation that vinyl chloride increases the risk of liver cirrhosis, which is a known risk factor for hepatocellular carcinoma, the findings from two large multicentre cohort studies provide convincing evidence that vinyl chloride causes hepatocellular carcinoma as well as angiosarcoma of the liver."

ATSDR Assessment

In the assessment of the evidence for causation, ATSDR placed high weight on assessments conducted by EPA, NTP and IARC as well as the meta-analyses. High weight was also given to a study that was considered of moderate utility by the NTP or pooled data from other studies. Information on possible mechanisms was also considered. Our assessment of the epidemiological evidence considered some of the viewpoints associated with Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if ≤ 1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding.

TCE:

Both meta-analyses found elevated summary RRs for TCE exposure and liver cancer. The EPA meta-analysis observed no evidence of between-study heterogeneity or publication bias. The summary RR for any exposure and the high exposure group were essentially the same, about 1.30 (Scott and Jinot 2011). However, the exposure-response evaluation in the EPA meta-analysis was severely limited by small numbers of highly exposed cases in the included studies.

Six occupational studies (four cohort and two case-control) have been published since the EPA meta-analysis was conducted. The NTP review of TCE and liver cancer considered four of these studies to be

of "low utility" (Bahr et al. 2011; Silver et al. 2014; Christensen et al. 2013 and Vlaanderen et al. 2013). One study was considered to have "low/moderate utility" (Lipworth et al. 2011), and one study was considered to have "moderate utility" (Hansen et al. 2013). The Hansen et al. 2013 pooled analysis of studies conducted in three Nordic countries obtained a RR for primary liver cancer of 1.93 (95% CI: 1.19, 2.95) that was similar for males and females. The RR increased with lag time when liver cancer was combined with cancer of the biliary passages (RR=2.09, 95% CI: 1.34, 3.11). The study evaluated urine TCA levels and found no increase in risk with increasing level. However, nearly half of the exposed cases were in the reference category with small numbers of cases in the higher urine-TCA levels. Other limitations were that a majority of the workers had only one or two urine-TCA measurements, and urine-TCA measures only recent TCE exposure (i.e., over the previous week). The study could not evaluate cumulative exposure or exposure duration. The Christensen et al. 2013 study obtained an elevated OR for "substantial" TCE exposure based on one exposed case (OR=2.5, 95% CI: 0.3, 25.0).

The four other occupational studies published after the EPA meta-analysis did not observe elevated risks, however each of these studies had serious limitations. The Lipworth et al. 2011 cohort study provided no information on TCE exposure levels although it was likely that exposures were low and of short duration since TCE use at the facility ended in 1966. Over 40% of the exposed cases had less than 1 year duration of exposure. There was also evidence of healthy worker effect bias with the SMRs for all cancers and liver cancer of 0.92 (95% CI: 0.96, 0.97) and 0.89 (95% CI: 0.57, 1.33), respectively. The Bahr et al. 2011 cohort study did not provide the total number of liver cancers, the number of exposed liver cancers, or the levels of TCE exposure. The authors acknowledged that strong healthy worker effect biases were present as the SMRs for all causes of death and for liver cancer were 0.76 (95% CI: 0.72, 0.79) and 0.43 (95% CI: 0.10, 1.84). Considerable exposure misclassification bias was likely because a generic JEM was used to determine exposure assignment. Healthy worker effect bias was also evident in the Silver et al. 2014 cohort study with an SMR for all cancers of 0.74 (95% CI: 0.71, 0.77) and the SMR for liver/biliary passages/gall bladder (calculated from data in the article) of 0.54 (95% CI: 0.39, 0.74). The study did not report exposure levels or the number of exposed cases, and TCE exposure prevalence was expected to be low. The exposure assessment was also limited by missing data on work histories. Finally, the Vlaanderen et al. 2013 case-control study was limited by low levels of TCE exposure and the use of a generic JEM that likely introduced considerable exposure misclassification bias. The authors acknowledged that the JEM used in this study was so poor that it was likely that a majority of those classified as exposed to TCE or PCE may have been unexposed to these chemicals.

The Camp Lejeune mortality studies found an increased risk of liver cancer among Marines/Navy personnel but not among civilian workers when compared to the Camp Pendleton cohorts (Bove et al. 2014a, b).

Mechanistic information: "Although species differences in sensitivity to the proposed modes of action are likely, no data suggest that trichloroethylene causes liver tumors in mice by mechanisms that are irrelevant to humans. Most of the hypothesized modes of action for liver tumors have some experimental support and are biologically plausible in humans and rodents." (NTP 2015, page 176). "It is likely that multiple mechanisms, potentially including immune dysregulation, epigenetic alterations, cytotoxicity and secondary oxidative stress, alteration of proliferation and/or apoptosis, may contribute to hepatocarcinogenesis." (Rusyn I et al. 2014).

Conclusion: The EPA meta-analysis observed an elevated risk for TCE and liver cancer with no evidence of publication bias or between-study heterogeneity. However, the meta-analysis was limited in its ability to evaluate exposure-response trends due to small numbers of highly exposed cases in the included studies. Several studies were conducted after the EPA meta-analysis but most had serious limitations, including low exposures, and biases due to exposure misclassification and/or healthy worker effect. ATSDR concludes that the epidemiological evidence by itself is sufficient to classify the causal association as at least equipoise. Combining the epidemiological evidence with the supporting evidence from animal studies and plausible mechanistic information, ATSDR concludes that there is **equipoise and above evidence for causation for TCE and liver cancer.**

PCE:

No meta-analysis has been conducted for PCE exposures and liver cancer. A limited number of epidemiological studies have evaluated PCE exposure and liver cancer. Two studies of dry cleaning workers did not find an elevated risk of liver cancer (Blair et al. 2003, Lynge et al. 2006). A third dry cleaning study found an elevated risk only among male workers (Selden et al. 2011). Cohort studies of workers exposed to PCE in other industries did not find an excess risk (Lipworth et al. 2011, Silver et al. 2014). One case-control study found elevated risks in the range of 1.1-1.2 (Vlaanderen et al. 2013).

Conclusion: The epidemiological evidence for PCE and liver cancer is insufficient to determine whether a positive association exists, given the conflicting and mostly negative findings in the dry cleaning and other occupational studies. Therefore, ATSDR concludes that there is **below equipoise evidence for causation for PCE and liver cancer.**

Vinyl Chloride:

The meta-analysis by Boffetta et al. 2003 indicated that vinyl chloride was associated not only with angiosarcoma of the liver but also hepatocellular carcinoma. Since the IARC review (IARC 2012), which concluded that there was convincing evidence that vinyl chloride exposure causes hepatocellular carcinoma as well as angiosarcoma of the liver, two recent studies, Hsieh et al. 2011 and Carreón et al. 2014, also found associations between occupational exposures to vinyl chloride and liver cancer. The Carreón et al. 2014, study also found an exposure-response trend for duration of exposure.

ATSDR concurs with the IARC (2012) assessment and concludes that there is **sufficient evidence for causation for vinyl chloride and hepatocellular carcinoma as well as angiosarcoma of the liver.**

Benzene

Because only one study evaluated occupational benzene exposure and liver cancer, the epidemiological evidence is insufficient to determine whether a positive association exists for benzene and liver cancer. Therefore, ATSDR concludes that there is **below equipoise evidence for causation for benzene and liver cancer.**

Pancreatic Cancer

Reference, type of cancer data, total # of subjects, follow-up period	Exposure[a] (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Ojajarvi 2001, 2007 **meta-analysis**	Metal degreasing Dry-cleaning & Laundry TCE Vinyl chloride PCE chlorinated hydrocarbon solvents		sRR=2.0 (1.2, 3.6) 6 studies 27 exposed cases sRR=1.4 (1.1, 2.4) 7 studies (3 incidence, 4 mortality) 83 exposed cases sRR=1.24 (0.79, 1.97) 5 studies (3 incidence, 2 mortality) 29 exposed cases (?)[**] sRR=1.17 (0.71, 1.91) 4 studies (all mortality studies) 85 exposed cases sRR=3.08 (0.63, 8.99) 1 study (cohort incidence study) 3 exposed cases sRR[w]=2.2 (1.31, 3.68) 20 studies		
Cohort Studies					
Anttila 1995[f] Incidence 3,089 TCE workers 849 PCE workers 1967-1992	TCE (urine TCA) PCE (blood PCE)	11 3	Any exposure: SIR=1.61 (0.81, 2.88) SIR=3.08 (0.63, 8.99)		Urine TCA (µmol/L) # cases <100 SIR=1.61 (0.59, 3.50) 6 100 + SIR=1.31 (0.27, 3.82) 3
Morgan 1998 Mortality 4,733 1950-1993	Aerospace workers TCE	11	Any exposure: SMR=0.76 (0.38, 1.37)	—	Exposure Intensity: (SMR) # cases Low: 0.95 (0.31, 2.22) 5 High: 0.66 (0.24, 1.43) 6
Ritz 1999 Mortality 3,814 1951-1989	Uranium Processing (JEM) TCE	 17 1 0		TCE Exposure duration (years) <2: Referent 2-10: 3.54 (0.45, 27.9) >10 0	
Raaschou-Nielsen 2003 Incidence 40,049 1964-1997	TCE (job title, plant air monitoring & urine TCA data)	 66 9	Any exposure: Men: SIR=1.1 (0.9, 1.4) Women: SIR=1.0 (0.5, 2.0)		
Zhao 2005 Mortality 6,044 1950-2001	TCE (JEM)		—	—	Cumulative intensity score # cases Medium: RR=1.13 (0.58, 2.21) 15 High: RR=0.35 (0.08,1.50) 2

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Radican 2008 Mortality 14,455 1953-2000	TCE (JEM) (Aircraft maintenance)	46 39 7	All: HR=1.06 (0.61, 1.84) Males: HR=0.91 (0.49, 1.68) Females: HR=1.71 (0.57, 5.12)	Cumulative exposure score (unit-yr) Men (HR) # cases 0-5: 0.97 (0.48, 1.97) 17 5-25: 0.74 (0.31, 1.76) 8 >25: 0.97 (0.46, 2.04) 14 Women (HR) # cases 0-5: 2.06 (0.51, 8.26) 3 5-25: 0 >25: 1.96 (0.55, 6.97) 4	Exposure Intensity Men (HR) # cases Low, Intermittent: 0.86 (0.45, 1.64) 27 Low, Continuous: 0.88 (0.44, 1.77) 19 Peak, Infrequent: 1.18 (0.49, 2.80) 8 Peak, Frequent: 0.96 (0.48, 1.93) 18 Women (HR) # cases Low, Intermittent: 1.53 (0.38, 6.13) 3 Low, Continuous: 0 Peak, Infrequent: 0 Peak, Frequent: 1.59 (0.45, 5.65) 4
Lipworth 2011 Mortality 5,443 (TCE) 5,830 (PCE) 1960-2008	Aircraft manufacturing TCE (JEM) PCE (JEM)	 53 39	Any exposure: SMR=0.93(0.70, 1.22) SMR=1.05 (0.75, 1.44)	–	–
Hansen 2013 Incidence 5,553 Finland:1967-2004 Sweden: 1958-2003 Denmark: 1968-2008	TCE (Urine TCA was used to identify workers ever exposed to TCE)	38 21 17	All: SIR=1.31 (0.93, 1.80) Females: SIR=2.18 (1.35, 3.34) Males: SIR=0.88 (0.51, 1.41)	–	–
Carreón 2014 Mortality 1,874 1960-2007	Vinyl chloride	11	SMR=1.90 (0.95, 3.40)		
Linet 2015 Mortality 73,789 exposed 35,504 unexposed 1972-1999	Benzene	45	RR=1.7 (1.0, 3.1)		
Buhagen 2016 Incidence 997 males 1960-2010	Train maintenance TCE (union employment list)	6	SIR=0.9 (0.4, 2.0)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Case-Control Studies					
Santibañez 2010 Incidence 161 cases 76 ductal adeno-carcinoma 455 controls 1995-1999	Chlorinated hydrocarbon solvents (JEM)	 1 5 1 4	Exposure intensity: All pancreatic cancer: "low" (≤0.83 ppm): OR=0.9 (0.1, 7.8) "high" (>0.83 ppm): OR=2.0 (0.6, 6.4) Ductal adenocarcinoma: "low" (≤0.83 ppm): OR=1.2 (0.1, 12.3) "high" (>0.83 ppm): OR=4.1 (1.1, 15.2)		
Antwi 2015 Incidence 2,092 cases 2,353 controls 2000-2014	Benzene Chlorinated hydrocarbons	105 279	OR=1.75 (1.29, 2.37) OR=1.63 (1.32, 2.02		
Dry Cleaning Workers Studies					
Blair 2003 Mortality 5,369 1948-1993	PCE (dry cleaning)	 28	Any exposure: SMR = 1.1 (0.7, 1.5)		Exposure intensity # cases Little/no: SMR=1.2 (0.7, 2.0) 14 Med/high: SMR=0.8 (0.4, 1.5) 11
Lynge 2006 Incidence 230 cases 975 controls 1970-2001	PCE (dry cleaning)	 57 32	Any exposure: RR=1.27 (0.90, 1.80) 4 countries; RR=1.38 (0.87, 2.20) 2 countries with most complete data on exposure	Employment duration (yrs.) # cases 0-1: RR=2.14 (0.76, 6.06) 6 2-4: RR=1.38 (0.54, 3.50) 7 5-9: RR=1.18 (0.62, 2.25) 14 ≥10: RR=1.20 (0.72, 1.99) 23 Unk: RR=2.44 (0.90, 6.66) 7	—
Calvert 2011 Mortality 1,704 618 PCE-only 1,086 PCE-plus 1940-2004	PCE (dry cleaning) (occupation, industry surveys, personal monitoring data)	22 18 4	All: SMR = 1.51 (0.95, 2.29) PCE-plus: SMR = 1.86 (1.10, 2.94) PCE-only: SMR = 0.82 (0.22, 2.10)		
Selden 2011 Incidence 9,440 1985-2006	Dry Cleaning & Laundry Workers (plant survey, work history)	34 10 24	All: SIR=1.30 (0.90, 1.81) Men: SIR=1.48 (0.71, 2.72) Women: SIR=1.24 (0.79, 1.84)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Drinking Water Studies					
Paulu 1999 Incidence 36 cases 622 controls 1983-1986	PCE-contaminated drinking water (modeled)	3	OR=0.6 (0.1,1.7)		
Bove 2014a (Camp Lejeune Marines/Navy) Mortality 154,932: Camp Lejeune 154,969: Camp Pendleton 1979-2008	VOC contaminated drinking water (modeled) vs U.S. population vs. Camp Pendleton	57	SMR=0.98 (0.74, 1.27) HR=1.36 (0.91, 2.02)		
Bove 2014b (Camp Lejeune Civilian workers) Mortality 4,647: Camp Lejeune 4,690: Camp Pendleton 1979-2008	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	12	SMR=1.02 (0.53, 1.78) HR = 0.54 (0.24, 1.20)	–	–

* Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.

** One included study did not report the number of exposed cases.

† Hierarchical Bayesian model combining information from studies that evaluated job titles only and information from a JEM . The number of exposed cases was not reported.

‡ This study was included in the Ojajarvi 2001meta-analysis but is listed here because of additional information on urine TCA.

RR: Risk Ratio

OR: Odds Ratio

SMR: Standardized Mortality Ratio

SIR: Standardized Incidence Ratio
95% CI: 95% Confidence Interval
sRR: Summary Risk Ratio
HR: Hazard Ratio
JEM: Job-exposure matrix
I: Incidence; M: mortality
VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)
Urine TCA: urine levels of trichloroacetic acid, a metabolite of TCE.

Note: Christensen et al. 2013 had no cases of pancreatic cancer with "substantial" exposure to PCE or TCE and is therefore not included in the table.
Note: Silver et al. 2014 did not evaluate chemical-specific results for pancreatic cancer and is therefore not included in the table.

Summary of NCI review of occupational exposures to chlorinated solvents and pancreatic cancer:

A review of the evidence for occupational exposures and pancreatic cancer by NCI (Andreotti G and Silverman DT 2012) concluded: "Chlorinated hydrocarbon exposure is one of the most researched and established occupational risk factors for pancreatic cancer." The review stated that, based on the meta-analyses of studies published between 1969 and 1998 of 20 populations in Europe, North America, and Asia (Ojajarvi et al. 2001, 2007) and a recent study (Santibañez et al. 2010), the authors concluded that: "...The strongest and most consistent findings linking occupational exposures with pancreatic cancer risk to date are for chlorinated hydrocarbons and PAHs." The authors specifically mentioned that pancreatic cancer was linked to TCE and PCE exposures as well as to dry cleaning and metal-related work including metal degreasing.

ATSDR Assessment

In the assessment of the evidence for causation, ATSDR considered the results of an early meta-analysis in the context of studies published after the meta-analysis was conducted. Our assessment of the epidemiological evidence considered some of the viewpoints associated with Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if ≤1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding.

TCE

The meta-analysis by Ojajarvi et al. 2001 found a summary RR of 1.24 (95% CI: 0.79, 1.97) based on five studies. A much higher summary RR of 2.0 (95% CI: 1.2, 3.6) was found for metal degreasing based on 6 studies (Ojajarvi et al. 2001). Eight cohort studies listed in the table were not included in the Ojajarvi et al. 2001 and 2007 meta-analyses. Of these studies, two observed elevated risks for TCE exposure and pancreatic cancer only in female workers (Radican et al. 2008, Hansen et al. 2013). Another cohort study found an SIR close to the null (SIR=1.1, 95% CI: 0.9, 1.4) in males and no elevation in females (Raaschou-Nielsen et al. 2003). Of the five other cohort studies, three observed no elevations in risk (Morgan et al. 1998; Lipworth et al. 2011; Buhagen et al. 2016), and two observed elevated risks among those in a lower exposure intensity or duration category but not in the higher category, although these analyses were limited by small numbers.

In the Camp Lejeune mortality studies, pancreatic cancer risk was elevated in the marine/Navy cohort but not in the civilian worker cohort when compared to the Camp Pendleton cohorts (Bove et al. 2014a, b).

Conclusion: Although the meta-analysis found an elevated risk for TCE and pancreatic cancer, the findings from subsequent studies have been mixed and not supportive of the meta-analysis. Therefore ATSDR concludes that there is **below equipoise evidence for causation for TCE and pancreatic cancer**.

PCE

The Ojajarvi et al. 2001 meta-analysis found an excess risk for dry cleaning and laundry worker studies (sRR=1.4, 95% CI: 1.1, 2.4) similar to that observed in two other dry cleaning studies that were published after the meta-analysis was conducted (Lynge et al. 2006 and Selden et al. 2011). The Ojajarvi et al 2001 paper also reported the finding from the Anttila et al. 1995 cohort study of PCE-exposed workers with exposure based on PCE blood measurements, (i.e., SIR of 3.08, 95% CI: 0.63, 8.99, based on three exposed cases). The Lipworth et al. 2011 cohort study of aircraft manufacturing workers observed an SMR near the null, but healthy worker effect bias was possible (e.g., the SMR for all cancers was 0.96, 95% CI: 0.89, 1.04) and exposures to PCE were much lower than those usually experienced in the dry cleaning industry.

In addition to the two dry cleaning studies published after the Ojajarvi et al. 2001 meta-analysis that found elevated risks (i.e., Lynge et al. 2006 and Selden et al. 2011), two other dry cleaning studies had mixed findings. In the Blair et al. 2003 cohort study, the SMR was near the null value (SMR=1.1, 95% CI: 0.7, 1.5) and an elevated risk was observed only for those with "little/no" exposure intensity. In the Calvert et al. 2011 cohort study, an elevated SMR was observed for workers in the "PCE-plus" category (i.e., workers who worked in a shop where PCE was the primary cleaning solvent, but also had a history of employment in shops where the primary solvent in use could not be identified) but not for workers in the "PCE-only" category. In this study, over 80% of the exposed pancreatic cancers were in the PCE-plus category with only four pancreatic cancers in the PCE-only category.

The drinking water study at Cape Cod did not observe an excess of pancreatic cancer (Paulu et al. 1999). The Camp Lejeune mortality study of Marines observed an excess of pancreatic cancer in the comparison with Camp Pendleton Marines but no excess risk was found in the study of civilian workers (Bove et al. 2014a, b).

Conclusion: Although there is some evidence of excess risk for pancreatic cancer from the meta-analysis, the findings from the dry cleaning worker studies are not consistent. In addition, the findings from the drinking water studies at Cape Cod and Camp Lejeune are not consistent. There is no animal data or mechanistic data to supplement the epidemiological evidence. Therefore, ATSDR concludes that there is **below equipoise evidence for causation for PCE and pancreatic cancer**.

Benzene

Two studies have evaluated occupational benzene exposures and pancreatic cancer (Linet et al. 2015, Antwi et al. 2015). Both studies found similar elevated risks of 1.7 (95% CI: 1.0, 3.1) and 1.75 (95% CI: 1.29, 2.37). However, the results of two studies are not sufficient to determine whether benzene exposure is a risk factor for pancreatic cancer. Therefore, ATSDR concludes that there is **below equipoise evidence for causation for benzene and pancreatic cancer.**

Vinyl Chloride

In the Ojajarvi et al.2001 meta-analysis, vinyl chloride had a summary RR of 1.17 (95% CI: 0.71, 1.91) based on four mortality studies. Since then, a cohort study of vinyl chloride workers observed an elevated risk for pancreatic cancer with an SMR of 1.9 (95% CI: 0.95, 3.40) (Carreón et al. 2014). However the epidemiological evidence is still too sparse to determine whether vinyl chloride is a risk factor for pancreatic cancer. Therefore, ATSDR concludes that there is **below equipoise evidence for causation for vinyl chloride and pancreatic cancer**.

Prostate cancer

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Cohort Studies					
Axelson 1994** Incidence 1,421 1958-1987	TCE (urine TCA)	26	Any exposure: SIR=1.25 (0.84, 1.84)	Years exposed # cases <2: SIR=1.19 (0.39, 2.78) 5 ≥2: SIR=1.27 (0.81, 1.94) 21	Urine TCA (mg/L) # cases <50: SIR=1.30 (0.65, 2.33) 11 50-99: SIR=0.91 (0.11, 3.28) 2 ≥100: SIR=2.40 (0.29, 8.67) 2
Anttila 1995** Incidence 1,698 1967-1992	TCE (urine TCA)	13	SIR=1.38 (0.73, 2.35)		Urine TCA (µmol/L) # cases <100 SIR=1.43 (0.62, 2.82) 8 100 + SIR=0.68 (0.08, 2.44) 2
Morgan 1998*** Mortality 2,555 1950-1993	Aerospace, TCE-exposed subcohort **Meta-analysis** (4 studies)	21 82	SMR = 1.18 (0.73, 1.80) mSMR=1.09 (0.87, 1.36)		Cumulative exposure: Low: RR= 1.72 (0.78, 3.80) 7 cases High: RR=1.53 (0.85, 2.75) 14 cases
Ritz 1999 Mortality 3,814 1951-1989	TCE (Uranium processing plant) (JEM)	24		TCE Exposure duration (years) <2: Referent 23 cases 2-10: 0 cases >10: RR=2.15 (0.28, 16.6) 1 case	Intensity of exposure, 15 year lag RR # cases "Light": 1.04 (0.40, 2.70) 8 "Moderate": 1.96 (0.25, 15.6) 1
Raaschou-Nielsen 2003 Incidence 40,049 1964-1997	TCE (job title, plant air monitoring & urine TCA data)	163	SIR=0.9 (0.79, 1.08)		
Boice 2006 Mortality 7,083 1948-1999	Aerospace workers TCE	8	Any exposure: SMR=0.82 (0.36, 1.62)		
Radican 2008 Mortality 10,730 1953-2000	Aircraft maintenance TCE (JEM)	116	Any TCE exposure: HR=1.20 (0.82, 1.76)	Cumulative exposure score (unit-yr): 0-5: HR=1.03 (0.65, 1.62) 41 cases 5-25: HR=1.33 (0.82, 2.15) 32 cases >25: HR=1.31 (0.84, 2.06) 43 cases	Exposure Intensity (HR) # cases Low, intermittent: 1.22 (0.82, 1.82) 87 Low, continuous: 1.30 (0.85, 1.99) 60 Peak, infrequent: 1.02 (0.57, 1.86) 16 Peak, frequent: 1.24 (0.81, 1.92) 52

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Lipworth 2011 Mortality 5,443 (TCE) 5,830 (PCE) 1960-2008	Aircraft manufacturing TCE (JEM) PCE (JEM)	 135 71	Any exposure: SMR = 1.11 (0.93, 1.31) SMR = 0.92 (0.72, 1.16)	Years exposed (RRs): TCE # cases <1: 0.80 (0.55, 1.16) 42 1-4: 1.17 (0.80, 1.70) 39 >4: 1.21 (0.84, 1.73) 51	 PCE # cases 0.87 (0.52, 1.45) 17 1.09 (0.72, 1.66) 28 0.73 (0.46, 1.17) 23
Hansen 2013 Incidence 3,776 Finland:1967-2004 Sweden: 1958-2003 Denmark: 1968-2008	TCE (Urine TCA was used to identify workers ever exposed to TCE)	128	SIR=0.96 (0.80, 1.14)		
Carreón 2014 Mortality 1,739 1960-2007	Vinyl chloride	4	SMR=0.59 (0.16, 1.51)		
Buhagen 2016 Incidence 997 males 1960-2010	Train maintenance TCE (union employment list)	46	SIR=0.9 (0.7, 1.2)		
Dry Cleaning Workers Studies					
Blair 2003 Mortality 1,320 1948-1993	PCE (dry cleaning)	17	SMR = 1.0 (0.6, 1.6)		
Selden 2011 Incidence 2,810 1985-2006	Dry Cleaning & Laundry Workers (plant survey, work history)	82	SIR=0.95 (0.76, 1.18)		
Case-Control Studies					
Krishnadasan 2007 Incidence 362 cases 1,805 controls 1988-1999	Aerospace/radiation TCE (JEM)			Duration x intensity score No Lag # cases Low/moderate: OR=1.3 (0.8, 2.1) 90 High: OR=2.1 (1.2, 3.9) 45	 20-year lag[§] OR=1.3 (0.8, 2.1) OR=2.4 (1.3, 4.4)

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Christensen 2013 Incidence 449 cases 533 controls 1979-1985	TCE PCE	14 7 9 9	Any exposure: OR=1.3 (0.6, 2.8) "Substantial": OR=1.1 (0.4, 3.1) Any exposure: OR=2.9 (0.8, 9.9) "Substantial": OR=6.0 (1.2, 30)		
Drinking Water Studies					
Bove 2014a (Camp Lejeune Marines/Navy) Mortality 146,893: Camp Lejeune 149,378: Camp Pendleton 1979-2008	VOC contaminated drinking water (modeled) vs U.S. population vs. Camp Pendleton	18	SMR = 1.73 (1.02, 2.73) HR = 1.23 (0.60, 2.49)	Any exposure (months) # cases 1-3: OR=0.6 (0.1, 4.8) 1 4-6: OR=1.7 (0.4, 8.1) 2 7-12: OR=0.9 (0.2, 4.2) 2 >12: OR=0.7 (0.2, 2.1) 6	
Bove 2014b (Camp Lejeune Civilian workers) Mortality 1,988: Camp Lejeune 2,309: Camp Pendleton 1979-2008	VOC contaminated drinking water (modeled) vs U.S. population vs. Camp Pendleton	10	SMR = 1.09 (0.52, 2.01) HR = 1.17 (0.49, 2.82)	6/10 deaths had exposure durations of 4 years or more.	Cumulative exposure (HR) # cases TCE: Medium: 2.6 (0.3, 25) 3 High: 2.4 (0.3, 21) 6 PCE Medium: 3.5 (0.4, 32) 4 High: 2.1 (0.2, 19) 5

* Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.

** Included in the Morgan et al. 1998 meta-analysis.

*** The Morgan et al. 1998 conducted a meta-analysis that included its own study and three other studies. The table reports both its study and its meta-analysis.

¶ The study did not provide the number of exposed cases for the 20-year exposure lag analysis.

RR: Risk Ratio
OR: Odds Ratio
SMR: Standardized Mortality Ratio

SIR: Standardized Incidence Ratio
95% CI: 95% Confidence Interval
mSMR: Summary SMR obtained through a meta-analysis
HR: Hazard Ratio
JEM: Job-exposure matrix
I: Incidence; M: mortality
VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)
Urine TCA: urine levels of trichloroacetic acid, a metabolite of TCE.

ATSDR Assessment:

In the assessment of the evidence for causation, ATSDR considered the results of an early meta-analysis in the context of studies published after the meta-analysis was conducted. Our assessment of the epidemiological evidence considered some of the viewpoints associated with Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if $\leq$1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding. Since prostate cancer is highly survivable, studies that evaluated incidence were considered to have higher utility than studies that evaluated mortality.

TCE

Of the ten occupational cohort studies that evaluated TCE exposure and prostate cancer, four did not observe an excess risk (Raaschou-Nielsen et al. 2003, Boice et al. 2006, Hansen et al. 2013 and Buhagen et al. 2016). One study observed an excess risk of 1.20 (95% CI: 0.82, 1.76) that increased to 1.31 (95% CI: 0.84, 2.06) among those with high cumulative exposure score (Radican et al. 2008). Another cohort study observed an SMR of 1.11 (95% CI: 0.93, 1.31) for any exposure to TCE and an SMR of 1.21 (95% CI: 0.84, 1.73) for exposure duration of more than four years (Lipworth et al. 2011). Morgan et al. 1998 observed elevated risks when cumulative exposure was evaluated but the trend was not monotonic. A meta-analysis of studies conducted by Morgan et al 1998, which included its own study and three other cohort studies, obtained a summary SMR of 1.09 (95% CI: 0.87, 1.36). A case-control study found a monotonic trend for an exposure metric that combined duration and intensity scores, with an OR of 2.4 (95% CI: 1.3, 4.4) for high exposure and a 20-year exposure lag (Krishnadasan et al. 2007). Another case-control study obtained an OR of 1.1 (95% CI: 0.4, 3.1) among workers with "substantial" exposure to TCE (Christensen et al. 2013).

Half of the occupational cohort studies evaluated prostate cancer mortality. Prostate cancer is highly survivable, with a 5-year survival percentage of nearly 99%. Therefore, studies that evaluated prostate cancer mortality were at a disadvantage, likely missing a majority of cases of the disease and impacting the precision of the effect estimate (i.e., width of the 95% confidence interval). Although four of the five occupational cohort mortality studies observed some increase in risk, in one study the increased risk was based on one exposed prostate cancer death (Ritz 1999) and the other three studies observed risks between 1.1 and 1.2. The Camp Lejeune studies also evaluated prostate cancer mortality and obtained elevated hazard ratios when comparing the Camp Lejeune cohorts to the Camp Pendleton cohorts. For the Camp Lejeune civilian workers, a majority of the prostate cancer deaths occurred among those with exposure durations of four years or more and risks were elevated among those with medium and high cumulative exposure although the trend was not monotonic. Among the seven studies that evaluated prostate cancer incidence, three studies did not observe an increased risk (Raaschou-Nielsen et al. 2003; Hansen et al. 2013; and Buhagan et al. 2016), one study observed a risk near the null value (Christensen

et al. 2013), and three observed an increased risk (Axelson et al. 1994; Anttila et al. 1995; and Krishnadasan et al. 2007).

Conclusion: ATSDR concludes that there is some evidence for a positive association between TCE and prostate cancer. However, the findings from the cohort and case-control studies are mixed with several studies finding no elevated risk. Therefore, ATSDR concludes that there is **below equipoise evidence for causation for TCE and prostate cancer**.

PCE

No meta-analyses have been conducted for PCE and prostate cancer. Few studies have evaluated PCE exposure and prostate cancer. Two cohort studies of dry cleaning workers have observed no excess in risk (Blair et al. 2003; Selden et al. 2011). A cohort mortality study of workers exposed to PCE in aircraft manufacturing also found no excess in risk (Lipworth et al. 2011). On the other hand, one case-control study found a great excess in risk among those with "substantial" exposure to PCE (OR=6.0, 95% CI: 1.2, 30) (Christensen et al. 2013). Given the paucity of epidemiological studies and the negative findings in the cohort studies, it is difficult to determine whether an association exists between PCE and prostate cancer or whether there is evidence against an association. On the other hand, the high excess risk observed in the case-control study provides some evidence against a conclusion that PCE does not cause prostate cancer.

Conclusion: ATSDR concludes that there is insufficient evidence to determine whether an association exists between PCE exposure and prostate cancer. Therefore, ATSDR concludes that there is **below equipoise evidence for causation for PCE and prostate cancer**.

Vinyl Chloride

One study evaluated vinyl chloride and prostate cancer and observed an SMR of 0.59 (95% CI: 0.16, 1.51) based on 4 exposed cases. Since only one study has been conducted, there is insufficient evidence to determine whether an association exists between vinyl chloride exposure and prostate cancer. Therefore, ATSDR concludes that there is **below equipoise evidence for causation for vinyl chloride and prostate cancer**.

Breast cancer

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Male breast cancer					
Raaschou-Nielsen 2003 Incidence 40,049 1964-1997	TCE (job title, plant air monitoring & Urine TCA data)	2	SIR=0.5 (0.1, 1.9)		
Hansen 2013 Incidence 3,776 Finland:1967-2004 Sweden: 1958-2003 Denmark: 1968-2008	TCE (urine TCA was used to identify workers ever exposed to TCE)	2	SIR = 2.11 (0.26, 7.60)		
Ruckart 2015 Incidence 71 cases 373 controls 1995-2013	Camp Lejeune contaminated drinking water (modeled) Camp Lejeune (y/n)	30	OR=1.14 (0.65, 1.97)		Modeled cumulative PCE (OR) # cases Low: 1.05 (0.14, 5.14) 2 High: 1.20 (0.16, 5.89) 2
Female breast cancer					
Cohort Studies					
Morgan 1998 Mortality 2,178 1950-1993	Aerospace, TCE-exposed subcohort	16	SMR=0.75 (0.43, 1.22)		Exposure Intensity: (SMR) # cases Low: 1.03 (0.51, 1.84) 11 High: 0.47 (0.15, 1.11) 5
Raaschou-Nielsen 2003 Incidence 40,049 1964-1997	TCE (job title, plant air monitoring & Urine TCA data)	145	SIR=1.1 (0.9, 1.2)		
Chang 2003 Mortality 86,868 1985-1997	Electronics factory Chlorinated organic solvents (PCE and TCE)	51	SMR=1.14 (0.85, 1.51)	Employment duration (yrs)¶ ≤1: SMR=1.08 31 cases <1 - ≤5: SMR=1.25 14 cases >5: SMR=1.32 6 cases	

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Chang 2005 Incidence 70,735 1979-1997	Electronics factory Chlorinated organic solvents (PCE and TCE)	215	SIR = 1.19 (1.03, 1.36)	Employment Duration (yrs.) # cases ≤1: SIR=1.20 (1.01, 1.41) 140 1-5: SIR=1.19 (0.90, 1.56) 54 >5-10: SIR=1.69 (1.02, 2.64) 19 >10: SIR=0.37 (0.04, 1.35) 2	
Radican 2008 Mortality 3,725 1953-2000	Aircraft maintenance TCE JEM)	26	Any TCE exposure: HR = 1.23 (0.73, 2.06)	Cumulative exposure score (unit-yr): 0-5: HR=1.57 (0.81, 3.04) 12 cases 5-25: HR=1.01 (0.31, 3.30) 3 cases >25: HR=1.05 (0.53, 2.07) 11 cases	Exposure Intensity (HR) # cases Low, intermittent: 1.92 (1.08, 3.43) 18 Low, continuous: 1.71 (0.79, 3.71) 8 Peak, infrequent: 1.18 (0.36, 3.86) 3 Peak, frequent: 1.08 (0.57, 2.02) 14
Costantini 2009 Incidence 679 1985-2000 Mortality 797 1950-2003	Shoe factory Benzene (JEM)	 24 10 14 12 3 9	Any exposure: SIR=1.20 (0.80, 1.79) latency (years): <30: SIR=1.41 (0.76, 2.62) ≥30: SIR=1.08 (0.64, 1.83) Any exposure: SMR=1.08 (0.62, 1.91) <30: SIR=0.59 (0.19, 1.81) ≥30: SIR=1.51 (0.79, 2.90)		Cumulative exposure (ppm-yr) # cases ≤40: SIR=1.16 (0.72, 1.86) 17 >40: SIR=1.30 (0.62, 2.73) 7 ≤40: SMR=0.96 (0.46, 2.02) 7 >40: SMR=1.31 (0.55, 3.15) 5
Lipworth 2011 Mortality 5,443 (TCE) 5,830 (PCE) 1960-2008	Aircraft manufacturing TCE (JEM) PCE (JEM)	 12 12	Any exposure: SMR = 1.03 (0.53, 1.80) for TCE SMR = 1.52 (0.78, 2.65) for PCE	Years exposed (RRs): TCE # cases <1: 0.82 (0.34, 1.98) 6 1-4: 0.31 (0.04, 2.32) 1 >4: 1.47 (0.50; 4.32) 4	PCE # cases 1.40 (0.59, 3.30) 6 0.25 (0.03, 1.81) 1 1.72 (0.53, 5.62) 3
Hansen 2013 Incidence 1,777 Finland:1967-2004 Sweden: 1958-2003 Denmark: 1968-2008	TCE (urine TCA was used to identify workers ever exposed to TCE)	86	SIR= 1.00 (0.80, 1.24)		
Linet 2015 Mortality 35,460 exposed 14,876 unexposed 1972-1999	Benzene	32	Exposed vs unexposed: RR=1.2 (0.6, 2.5)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Dry Cleaning Workers Studies					
Blair 2003 Mortality 4,049 1948-1993	PCE (dry cleaning)	68	SMR = 1.0 (0.8, 1.3)		Exposure intensity: # cases Little/no: SMR=0.8 (0.6, 1.2) 30 Med/high: SMR=1.2 (0.8, 1.7) 29
Selden 2011 Incidence 4,479 1985-2006	Dry Cleaning: PCE subcohort (plant survey, work history)	140	SIR=0.85 (0.72, 1.00)		
Calvert 2011 Mortality 1,112 412 PCE only 700 PCE plus 1940-2004	PCE (dry cleaning) (occupation, industry surveys, personal monitoring data)	28 10 18	All: SMR=1.05 (0.70, 1.52) PCE only: SMR=1.06 (0.51, 1.94) PCE plus: SMR=1.05 (0.62, 1.66)		
Case-Control Studies					
Peplonska 2010 Incidence 2383 cases 2502 controls 2000-2003	Benzene	115	Any exposure: OR=1.0 (0.8, 1.3)	Duration of Exposure (yrs) # cases >0-5: OR=1.1 (0.7, 1.7) 42 >5-10: OR=1.4 (0.7, 2.5) 25 >10: OR=0.8 (0.6, 1.2) 48	Exposure Intensity (mg/m^3) # cases >0-1: OR=1.0 (0.7, 1.3) 92 >1: OR=1.2 (0.7, 2.2) 23 Cumulative Exposure Low: OR=1.0 (0.7, 1.5) 58 High: OR=1.0 (0.7, 1.4) 57
Oddone 2014 Incidence 51 cases 103 controls 2002-2009	"Chlorinated solvents" (TCE)**	16	Any exposure: OR=1.65 (1.04, 2.62)	Any exposure, Duration ≥10 years, OR=2.1 (1.2, 3.7) 14 cases	

Reference, type of cancer data, total # of subjects, follow-up period	Exposure^ (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Glass 2015 Incidence 1202 cases 1785 controls 2009-2011	Benzene (any exposure)	75	OR = 1.08 (0.80, 1.47)		
		26	OR = 1.53 (0.84, 2.80) for premenopausal women		
		49	OR = 0.96 (0.67, 1.38) for post-menopausal women		
	Chlorinated Solvents*** (any exposure)	203	OR = 1.05 (0.69, 1.61)		
		12	OR = 1.47 (0.62, 3.45) for premenopausal women		
		25	OR = 0.94 (0.57, 1.54) for post-menopausal women		
Drinking Water Studies					
Gallagher 2011 Incidence 920 cases 1293 controls 1983-1993	PCE in drinking water (modeled)	 37 13	>90th percentile exposure and 13-year latency: OR=1.5 (0.9, 2.5) OR=2.0 (0.8, 4.8) using LOESS smoothing		
Bove 2014a (Camp Lejeune Marines/Navy) Mortality 8,038: Camp Lejeune 5,591: Camp Pendleton 1979-2008	VOC contaminated drinking water (modeled) vs U.S. population vs. Camp Pendleton	10	SMR=0.51 (0.24, 0.94) HR=0.93 (0.34, 2.50)		
Bove 2014b (Camp Lejeune Civilian workers) Mortality 2,659: Camp Lejeune 2,381: Camp Pendleton 1979-2008	VOC contaminated drinking water (modeled) vs U.S. population vs. Camp Pendleton	21	SMR=0.98 (0.61, 1.50) HR = 1.21 (0.58, 2.51)		

* Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.

¶ No confidence intervals were reported.

** The study reported results for "chlorinated solvents", but in a footnote stated that exposure was to TCE.

*** Tables listing number of chlorinated solvent exposed cases may be in error.

RR: Risk Ratio

OR: Odds Ratio

SMR: Standardized Mortality Ratio

SIR: Standardized Incidence Ratio

95% CI: 95% Confidence Interval

HR: Hazard Ratio

JEM: Job-exposure matrix

VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)

Urine TCA: urine levels of trichloroacetic acid, a metabolite of TCE.

ATSDR Assessment:

ATSDR's assessment of the epidemiological evidence considered some of the viewpoints associated with Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if ≤1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding. Since breast cancer is highly survivable, studies that evaluated incidence were considered to have higher utility than studies that evaluated mortality. One study that evaluated possible susceptible populations (i.e., pre-menopausal vs post-menopausal women) was also considered to have higher utility.

TCE

No meta-analyses have been conducted of TCE exposure and male or female breast cancer. Only three studies have been conducted that evaluated male breast cancer and TCE exposure. The two cohort studies (Raaschou-Nielsen et al. 2003 and Hansen et al. 2013) had two exposed cases each and conflicting findings, and the Camp Lejeune case-control study observed an overall OR of 1.14 (95% CI: 0.65, 1.97) (Ruckart et al. 2015).

Of the five cohort studies that evaluated female breast cancer and TCE exposure, two did not observe an excess risk (Morgan et al. 1998 and Hansen et al. 2013), one observed an elevated risk only among those workers exposed for more than 4 years (RR=1.47, 95% CI: 0.50, 4.32) (Lipworth et al. 2011) and two observed elevated risks in the range of 1.1 (95% CI: 0.9, 1.2, Raaschou-Nielsen et al. 2003) and 1.2 (95% CI: 0.7, 2.1, Radican et al. 2008). One case-control study obtained an OR of 1.65 (95% CI: 1.04, 2.62) for any TCE exposure which increased to 2.1 (95% CI: 1.2, 3.7) for those with exposure duration of at least 10 years (Oddone et al. 2014). Female breast cancer is highly survivable with a five-year survival percentage of nearly 90%. It is likely that the three cohort mortality studies missed a majority of breast cancer cases. Nevertheless, the findings from both the incidence and the mortality studies were evenly mixed. The Camp Lejeune mortality study of Marines did not observe an excess risk whereas the mortality study of civilian workers observed an excess risk of 1.21 (95% CI: 0.58, 2.51) when compared to civilian workers at Camp Pendleton (Bove et al. 2014a, b).

Conclusion: The epidemiological evidence for male breast cancer and TCE exposure is too sparse to determine whether an association exists. The results from the studies of female breast cancer and TCE exposure are inconsistent. Therefore, ATSDR concludes that there is **below equipoise evidence for causation for TCE and breast cancer.**

PCE

No meta-analyses have been conducted for PCE and breast cancer. No occupational studies evaluated PCE exposure and male breast cancer. Three occupational cohort studies have evaluated dry cleaning workers and female breast cancer. One study of breast cancer incidence found no excess in risk (Selden et al. 2011). One study of breast cancer mortality found an excess risk (SMR=1.2, 95% CI: 0.8, 1.7) among those with medium or high exposure and no excess risk among those who worked at pick-up stations where no dry cleaning occurred (i.e., the only exposure was due to off-gassing from dry cleaned

garments) and who were assigned as having "little/no exposure" (Blair et al. 2003). The third dry cleaning study found a risk close to the null value (SMR=1.06, 95% CI: 0.51, 1.94)) (Calvert et al. 2011). One cohort study of aircraft manufacturing workers observed an SMR of 1.52 (95% CI: 0.78, 2.65) for any PCE exposure and a RR of 1.72 (95% CI: 0.53, 5.62) for those with more than 4 years of exposure (Lipworth et al. 2011).

In the Cape Cod drinking water study, exposure to PCE-contaminated drinking water resulted in an increased risk (OR=1.5, 95% CI: 0.9, 2.5) among those with the highest cumulative exposures (Gallagher et al. 2011).

Animal and mechanistic information: Rats exposed by inhalation to PCE had an increased incidence of fibroadenoma of the mammary gland, although rats exposed by gavage did not have an increased incidence (IARC 2014).

Conclusion: The results from the few cohort studies of female breast cancer and PCE exposure are mixed. The findings from the Cape Cod drinking water study and the cohort study of aircraft manufacturing workers provide some support for an association. However, the overall evidence for PCE and breast cancer is limited by the paucity of studies and the mixed findings in the dry cleaning worker studies. Therefore, ATSDR concludes that there is **below equipoise evidence for causation for PCE and breast cancer.**

Chlorinated Solvents

Two occupational studies that evaluated chlorinated solvents as a group are included in the table for completeness and provide only weak evidence for an association between female breast cancer and either TCE or PCE, separately or as a mixture. One cohort study (Chang et al. 2003, 2005) and one case-control study (Glass et al. 2015) evaluated chlorinated solvents as a group and female breast cancer. The cohort study evaluated a workforce likely exposed to both TCE and PCE and possibly other solvents. The study found an SIR of 1.19 (95% CI: 1.03, 1.36) for any exposure, an SIR of 1.69 (95% CI: 1.02, 2.64) for employment duration of >5-10 years, but the SIR for >10 years of employment was below the null value (SIR=0.37, 95% CI: 0.04, 1.35, based on 2 exposed cases) (Chang et al. 2005). For breast cancer mortality, the cohort study observed an SMR of 1.14 (95% CI: 0.85, 1.51) for any exposure and a monotonic trend in the SMRs for employment duration (SMR=1.32 for >5 years of employment) (Chang et al. 2003). One case-control study found an excess risk exclusively among pre-menopausal women (Glass et al. 2015). This study indicated that the predominant chlorinated solvent exposure among the women in the study was due to work as a dry cleaner.

Benzene

No meta-analyses have been conducted for benzene and breast cancer. Two occupational cohort studies (Constantini et al. 2009, Linet et al. 2015) and two case- control studies (Peplonska et al. 2010, Glass et al. 2015) have evaluated benzene exposure and breast cancer. One cohort study observed an SIR of 1.30 (95% CI: 0.62, 2.7) in the high cumulative exposure group (Constantini et al. 2009), and the other observed a RR of 1.2 (95% CI: 0.6, 2.5) for any exposure (Linet et al. 2015). One case-control study found an excess risk exclusively among pre-menopausal women (Glass et al. 2015). A second case-

control study found no elevated risk among those with any benzene exposure but did observe elevated risks for those with higher exposure intensity (OR=1.2, 95% CI: 0.7, 2.2) (Peplonska et al. 2010).

Conclusion: The few studies that have been conducted of benzene exposure and breast cancer have found excess risks. However, the paucity of studies of benzene exposure and breast cancer leads ATSDR to conclude that there is **below equipoise evidence for causation for benzene and breast cancer.**

Bladder cancer

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Vlaanderen 2014 **meta-analysis**	PCE (Dry cleaning worker studies)	463 139	sRR = 1.08 (0.82, 1.42) for 3 PCE workers studies (2 case-control incidence studies, 1 cohort mortality study) sRR = 1.47 (1.16, 1.85) for 7 dry cleaning workers studies (5 incidence, 2 mortality)		
Cohort Studies					
Axelson 1994 Incidence 1,670 1958-1987	TCE (urine TCA)	8	SIR=1.02 (0.44, 2.00)		
Anttila 1995 Incidence 3,089 1967-1992	TCE (urine TCA)	5	SIR=0.82 (0.27, 1.90)		
Morgan 1998 Mortality 4,733 1950-1993	Aerospace TCE subcohort	8	SMR=1.36 (0.59, 2.68)		Cumulative Exposure (SMR) # cases Low TCE: 0.51 (0.01, 2.83) 1 High TCE: 1.79 (0.72, 3.69) 7 Cumulative & Peak Exposure (RR) # cases Peak (med/high): 1.41 (0.52, 3.81) 5 Low cumulative: 0.69 (0.09, 5.36) 1 High cumulative. 2.71 (1.10, 6.65) 7
Raaschou-Nielsen 2003 Incidence 40,049 1964-1997	TCE (job title, plant air monitoring & urine TCA data)	203 17	Any exposure: Men: SIR=1.0 (0.9, 1.2) Women: SIR=1.6 (0.9, 2.6)		
Zhao 2005 Incidence 6,044 1950-2001	Aerospace TCE (JEM)			Cumulative exposure score (RRs) Zero lag # cases Medium: 1.8 (0.6, 5.2) 19 High: 3.8 (1.0, 14.8) 11	20 year lag # cases 1.8 (0.6, 5.1) 20 3.7 (0.9, 15.5) 10
Radican 2008[#] Mortality 10,730 male workers 1953-2000	Aircraft maintenance TCE (JEM)	24	Any TCE exposure: HR=1.05 (0.47, 2.35) (males only)	Cumulative exposure score (unit-yr): 0-5: HR=0.96 (0.37, 2.51) 9 cases 5-25: HR=1.77 (0.70, 4.52) 10 cases >25: HR=0.65 (0.21, 1.98) 5 cases	Exposure Intensity # cases Low, intermittent HR=1.03 (0.44, 2.41) 17 Low, continuous HR=1.32 (0.55, 3.18) 14 Peak, infrequent HR=0.59 (0.12, 2.78) 2 Peak, frequent HR=0.82 (0.30, 2.19) 8

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Lipworth 2011 Mortality 5,443 (TCE) 5,830 (PCE) 1960-2008	Aircraft manufacturing TCE (JEM) PCE (JEM)	 35 17	 SMR=1.03 (0.72, 1.43) SMR=0.84 (0.49, 1.35)	**Note:** PCE 8hr TWA, mean=9.5 ppm, median=3 ppm (compared to dry cleaning: mean=57 ppm)	
Hansen 2013 Incidence 5,553 Finland:1967-2004 Sweden: 1958-2003 Denmark: 1968-2008	TCE (urine TCA was used to identify workers ever exposed to TCE)	54 4	SIR=1.21 (0.91, 1.58) males SIR=0.77 (0.21, 1.96) females		
Silver 2014 Mortality 34,494 1969-2009	Microelectronics plant TCE (JEM) PCE (JEM)	48			Cumulative exposure (5 exposure-yrs) HR=0.04 (0.00, 5.71) HR=0.89 (0.37, 2.13)
Carreón 2014 Mortality 1,874 1960-2007	Vinyl chloride	 4	Any exposure: SMR=1.55 (0.42, 3.98)		
Linet 2015 Mortality 73,789 exposed 35,504 unexposed 1972-1999	Benzene	18	RR=0.9 (0.4, 2.2)		
Buhagen 2016 Incidence 997 males 1960-2010	Train maintenance TCE (union employment list)	11	SIR=0.7 (0.4, 1.3)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure[^] (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Case-Control Studies					
Pesch 2000[**] (case-control) Incidence 1035 cases 4298 controls 1991-1995	JEM		Females were not assessed for TCE or PCE exposure by JTEM. Cutpoints: Medium=≥30th percentile High= ≥60th percentile Substantial=>90th percentile	Cumulative Exposure Indices: OR (# cases): Medium / High / Substantial TCE (JEM) Males: 1.1 (0.8,1.3) (154) / 1.1 (0.9,1.4) (182) / 1.3 (0.9,1.7) (68) Females: 1.0 (0.6,1.7) (21) / 1.6 (1.0,2.5) (32) / 0.6 (0.2,2.3) (3) TCE (JTEM) Males: 0.8 (0.6, 1.2) (47) / 1.3 (0.9,1.7) (74) / 1.8 (1.2,2.7) (36) PCE (JEM) Males: 1.1 (0.9,1.3) (162) / 1.2 (1.0,1.5) (172) / 1.4 (1.0,1.9) (71) Females: 1.8 (1.0,3.0) (21) / 1.0 (0.6,1.9) (16) / 0.7 (0.2,2.5) (3) PCE (JTEM) Males: 1.0 (0.7,1.5) (37) / 1.2 (0.8,1.7) (47) / 1.8 (1.1,3.1) (22) Benzene (JEM) Males: 1.1 (0.8,1.4) (95) / 0.9 (0.7,1.2) (70) / 1.5 (1.0,2.1) (47) Females: 1.2 (0.7,2.0) (21) / 1.5 (0.9,2.8) (18) / 1.4 (0.6,3.3) (8) Benzene (JTEM) Males: 0.7 (0.5,1.0) (51) / 1.0 (0.7,1.3) (71) / 1.4 (0.9,2.1) (37) Females: 0.4 (0.1,1.8) (2) / 0.4 (0.1,1.2) (3) / 0.8 (0.2,3.7) (2)	
Christensen 2013 Incidence 484 cases 533 controls 1979-1985	TCE PCE	10 5 2 2	Any exposure: OR=0.7 (0.3, 1.7) Substantial: OR=0.6 (0.2, 1.7) Any exposure: OR=0.5 (0.1, 3.0) Substantial: OR=0.9 (0.1, 7.3)		
Dry Cleaning Worker Studies					
Blair 2003[***] Mortality 5,369 1948-1993	Dry Cleaning	12	Any exposure: SMR=1.3 (0.7, 2.4)	Entering dry cleaning union: <1960: SMR=1.1 (0.5, 2.0) 9 cases ≥1960: SMR=2.9 (0.6, 9.5) 3 cases Duration in the dry cleaning union: <4.4 years; SMR=2.1[¶] ≥4.4 years: SMR=0.9[¶]	Exposure Intensity: # cases Little/no: SMR=1.4 (0.4, 3.2) 5 Med/high: SMR=1.5 (0.6, 3.1) 7
Lynge 2006[***] Incidence 282 cases 1,196 controls 1970-2001	Dry Cleaning	93 62	Any exposure RR=1.44 (1.1, 1.9) 4 countries RR=1.69 (1.2, 2.4) 2 countries with most complete data on exposure	Duration of employment: ≤1 yr OR=1.50 (0.57, 3.96) 6 cases 2-4 yrs OR=2.39 (1.09, 5.22) 10 cases 5-9 yrs OR=0.91 (0.52, 1.59) 17 cases ≥10 yrs OR=1.57 (1.07, 2.29) 53 cases Unknown OR=1.97 (0.64, 6.05) 6 cases	

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Calvert 2011*** Mortality 1,704 618 PCE-only 1,086 PCE-plus 1940-2004	Dry Cleaning (occupation, industry surveys, personal monitoring data)	10 0 10	All: SMR=1.81 (0.87, 3.33) PCE only: No cases PCE plus: SMR=2.59 (1.24, 4.76)	9 of 10 cases had duration of ≥5 years and latency of ≥20 years (SMR=4.08 (2.13, 7.12)	
Selden 2011 Incidence 9,440 1985-2006	Dry Cleaning and Laundry Workers: (plant survey, work history)	 38 18 20	Any exposure All: SIR=0.92 (0.65, 1.26) Men: SIR=0.86 (0.51, 1.36) Women: SIR=0.98 (0.60, 1.52)		
Drinking Water Studies					
Aschengrau 1993 (case-control) Incidence 61 cases 852 controls 1983-1986	PCE in drinking water (modeled)	13	OR = 1.55 (0.74, 3.01)	**Note: High exposure (>90th percentile) was in range of Camp Lejeune drinking water levels.**	Cumulative exposure: # cases Low: OR=1.16 (0.48, 2.48) 9 High: OR=6.04 (1.32, 21.84) 4
Bove 2014a (Camp Lejeune Marines/Navy) Mortality 154,932: Camp Lejeune 154,969: Camp Pendleton 1979-2008	VOC contaminated drinking water vs U.S. population vs Camp Pendleton	11	SMR=0.84 (0.42, 1.51) HR=0.76 (0.34, 1.71)		
Bove 2014b (Camp Lejeune Civilian workers) Mortality 4,647: Camp Lejeune 4,690: Camp Pendleton 1979-2008	VOC contaminated drinking water vs U.S. population vs Camp Pendleton	2	SMR=0.53 (0.06, 1.92) HR=0.65 (0.12, 3.65)		

* Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.

Ψ There were only 2 bladder cancer deaths among female workers.

** The study was included in the Vlaanderen et al. 2014 meta-analysis. It is included in the table because of additional information on TCE and benzene as well as information on exposure intensity.

*** The study was included in the Vlaanderen et al. 2014 meta-analysis. It is included in the table because of information on exposure duration and/or cumulative exposure.

¶ Median years in the union was 4.4. The study did not provide confidence intervals or the number of bladder cancer deaths for this analysis.

JEM: job-exposure matrix

JTEM: job-task exposure matrix

RR: Risk Ratio

OR: Odds Ratio

SMR: Standardized Mortality Ratio

SIR: Standardized Incidence Ratio

95% CI: 95% Confidence Interval

sRR: Summary Risk Ratio

HR: Hazard Ratio

I: Incidence; M: mortality

VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)

Urine TCA: urine levels of trichloroacetic acid, a metabolite of TCE.

Summary of EPA and IARC reviews of PCE and bladder cancer:

EPA Toxicological Review of Tetrachloroethylene, 2012

EPA identified 32 epidemiological studies reporting data on bladder cancer and PCE exposure. Its review concluded: "In conclusion, the pattern of results from this collection of studies is consistent with an elevated risk for tetrachloroethylene of a relatively modest magnitude. The effect estimates from four of the five studies with the relatively high quality exposure-assessment methodologies provide evidence of an association, with relative risks of 1.44 to 4.03 (Calvert et al. , 2011; Lynge et al. , 2006; Blair et al. , 2003; Pesch et al. , 2000b; Aschengrau et al. , 1993). ... Confounding by smoking is an unlikely explanation for the findings..." (EPA 2012, pp. 4-100, 4-101).

A subsequent review article by EPA researchers who authored the toxicological review concluded: "The epidemiological evidence from cohort and case–control studies provides evidence of associations between PCE exposure and bladder cancer, non-Hodgkin lymphoma, and multiple myeloma in adults. Of these, bladder cancer and non-Hodgkin lymphoma were considered to have the strongest databases on the basis of the relative consistency of an observed association among studies with the higher quality exposure measurement and indication of increasing risk with increasing exposure among the studies using a cumulative exposure metric." (Guyton KZ et al. 2014). The review emphasized that the studies of dry cleaning workers were useful since the workers "are unlikely to have been exposed to other occupational bladder carcinogens." (Guyton KZ et al. 2014).

"...PCE is characterized as "likely to be carcinogenic to humans" (U.S. EPA 2012). This characterization is based on suggestive evidence of carcinogenicity in epidemiological studies and conclusive evidence that the administration of PCE, either by ingestion or by inhalation to sexually mature rats and mice, increases tumor incidence." (Guyton et al. 2014)

IARC Monograph 106 (IARC 2014)

In its assessment of the human data for the carcinogenicity of PCE, IARC focused on studies of dry cleaners (i.e., not mixed with laundry workers) and studies that distinguished worker exposures to PCE (IARC 2014). IARC concluded: "All eight studies that evaluated employment in dry-cleaning showed positive associations with bladder cancer. .... While positive associations with bladder cancer were observed in several cohort and case-control studies, and smoking was adequately controlled for in the majority, employment in dry-cleaning was in most cases the only indicator of exposure to tetrachloroethylene, the number of exposed cases was small, and support for an exposure-response relationship was lacking." (p. 326, IARC Monographs – 106, 2014). It further concluded: "The bladder has been identified as a target organ for tetrachloroethylene-induced carcinogenesis in humans; however there are no mechanistic studies available to support this. ... There is *limited* evidence in humans for the carcinogenicity of tetrachloroethylene. Positive associations have been observed for cancer of the bladder." (p. 329). "Tetrachloroethylene is *probably carcinogenic to humans (Group 2A)*." (p. 329).

ATSDR Assessment

In the assessment of the evidence for causation, ATSDR placed high weight on assessments conducted by EPA and IARC as well as the meta-analysis of PCE and bladder cancer. High weight was also given to studies that provided mechanistic information. Our assessment of the epidemiological evidence considered some of the viewpoints associated with Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if ≤1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding.

PCE

The ATSDR assessment of the evidence for causality for PCE and bladder cancer weighted strongly the assessments by EPA and IARC and the meta-analysis conducted by Vlaanderen et al. 2014. Subsequent to the assessments by EPA (EPA 2012) and IARC (IARC 2014), an IARC workgroup comprising those who were authors of the IARC monograph as well as additional researchers conducted a meta-analysis of PCE and bladder cancer focused on dry cleaning studies but also evaluating studies of other workers exposed to PCE (Vlaanderen et al. 2014). The researchers reported that there was no evidence of between-study heterogeneity or publication bias.

Seven studies of dry cleaning workers (3 cohort and 4 case-control) were included in the Vlaanderen et al. 2014 meta-analysis with a total of 139 exposed cases. The summary RR was 1.47 (95% CI: 1.16, 1.85). Among the case-control studies, all of which adjusted for smoking, the summary RR was 1.50 (95% CI: 0.8, 2.84) which was similar to the summary RR among the cohort studies of 1.46 (95% CI: 1.14, 1.87), indicating that the cohort studies were unlikely to be biased by uncontrolled confounding by smoking.

Three key dry cleaning cohort studies conducted by NCI, NIOSH and Nordic researchers that were included in the meta-analysis found positive associations. The Nordic study (Lynge et al. 2006) obtained RRs of 1.44 (1.07, 1.93) and 1.69 (1.18, 2.43) for all Nordic countries and analyses restricted to Denmark and Norway, respectively. Denmark and Norway had the most complete information on employment with fewer than 2% of the workers being unclassified concerning employment in dry cleaning compared to 35% unclassifiable among Swedish workers and 41% unclassifiable among Finland workers.

The NCI dry cleaning worker study (Blair et al. 2003) obtained an SMR of 1.3 (0.7, 2.4). The NIOSH dry cleaning worker study (Calvert et al. 2011) obtained an SMR of 2.59 (1.24, 4.76) for workers who worked in shops where PCE was the primary cleaning solvent but also worked in shops for which the primary solvent was unidentified (but likely PCE).

These three key cohort studies of dry cleaning workers had some information on exposure-response trends. The NCI study (Blair et al. 2003) found a slightly higher SMR for those with medium/high exposure (SMR=1.5, 95% CI: 0.6, 3.1) compared to those with little exposure (SMR=1.4, 95% CI: 0.4, 3.2) with wide confidence intervals due to small numbers of cases in the two exposure categories. The NCI study also noted that the elevation in bladder cancer mortality risk coincided with the introduction

of PCE in US dry cleaning facilities by 1960 (Blair et al. 2003). The NIOSH study (Calvert et al. 2011) observed an elevated SMR for workers exposed for at least 5 years (SMR=4.08, 95% CI: 2.13, 7.12) but no elevated SMR among those exposed for <5 years. Finally, a study of Nordic dry cleaning workers (Lynge et al. 2006) found elevated RRs for those with up to 1 year duration of employment (RR=1.50, 95% CI: 0.57, 3.96), 2-4 years duration of employment (RR=2.39, 95% CI: 1.09, 5.22) and 10 or more years duration of employment (RR=1.57, 95% CI: 1.07, 2.29) but not for those with 5-9 years duration of employment (RR=0.91, 95% CI: (0.52, 1.59).

The Vlaanderen et al. 2014 meta-analysis also evaluated one cohort study and two case-control studies of PCE-exposed workers for a total of 463 exposed cases. One case-control study (Christensen et al. 2013) had only two cases with PCE exposure and is of low utility. The cohort study (Lipworth et al. 2011) of aircraft manufacturing workers had 17 bladder cancer deaths exposed to PCE with an SMR of 0.84. NTP considered this study of relatively low utility because it did not provide information on exposure levels, the duration of exposure was likely short, and it did not evaluate an exposure-response trend (NTP 2015). From information provided in an earlier article about the exposure assessment of this plant, the measured levels of PCE in the air during an 8 hour shift were considerably lower (i.e., 1/6th the level) than those typically found in dry cleaning establishments. The other case-control multicenter study of the German population (Pesch et al. 2000) found monotonic exposure-response trends for exposure indices based on duration, intensity and probability of exposure (using a job exposure matrix and a job-task exposure matrix) for male workers. For "substantial exposure" using the exposure index based on the job-task exposure matrix, the OR was 1.8 (95% CI: 1.1, 3.1). (There were small numbers of female cases in the high exposure category.)

Based on the findings in the German case-control study (Pesch et al. 2000) and the three dry cleaning cohort studies, the authors of the meta-analysis concluded that there was some evidence of an exposure-response trend: "Our meta-analysis demonstrates an increased risk of bladder cancer in dry cleaners, reported in both cohort and case-control studies, and some evidence for an exposure-response relationship. Although dry cleaners incur mixed exposures, tetrachloroethylene could be responsible for the excess risk of bladder cancer because it is the primary solvent used and it is the only chemical commonly used by dry cleaners that is currently identified as a potential bladder carcinogen." (Vlaanderen et al. 2014).

The Camp Lejeune mortality studies provided an initial look at the disease situation among adults exposed at the base (Bove et al. 2014a, b). The cohorts of Marines and civilian workers were too young at the end of follow-up to effectively evaluate cancer mortality, especially bladder cancer. According to the American Cancer Society, bladder cancer occurs mainly in older people with the average age at the time of diagnosis of 73 years and about 90% diagnosed after the age of 55. However, the median ages at the end of follow-up for Marines/Navy personnel and civilian workers at Camp Lejeune were 49 years and 58 years, respectively, with most members of these cohorts under the age of 65 years at the end of follow-up. Because of their young age at the end of follow-up, a strong healthy worker/veteran bias would be expected, especially among Marines. In the study of civilian workers, there were only two cases of bladder cancer in the Camp Lejeune cohort and the SMR was 0.53 (95% CI: 0.06, 1.92) indicating a strong healthy worker effect for that cancer (Bove et al. 2014b). In the Camp Lejeune study of Marines and Navy personnel, there were 11 cases in the Camp Lejeune cohort with an SMR of 0.84 (95% CI: 0.42, 1.51) indicating a strong healthy veteran effect (Bove et al. 2014a). Other causes of death occurring in the Camp Lejeune marine cohort also indicated a strong healthy veteran effect, for example, all causes of death (SMR=0.83, 95% CI:0.81, 0.84) and all cancers (SMR=0.85, 95% CI: 0.85, 0.90). Because bladder cancer is highly survivable with a 5-year survival percentage of over 77%, a

comprehensive evaluation of bladder cancer at Camp Lejeune should be based on incidence data rather than mortality data. A future cancer incidence study of Marines/Navy personnel and civilian workers at Camp Lejeune is underway.

The study of PCE-contaminated drinking water in Cape Cod, MA and bladder cancer incidence found an elevated odds ratio (OR) and an exposure response trend (Aschengrau et al. 1993). The odds ratio for exposures >90th percentile was 6.04 (1.32, 21.84). The PCE levels corresponding to the 90th percentile were within the range estimated at Hadnot Point and Tarawa Terrace (Bove et al. 2014a).
Although there are animal data indicating that PCE causes neoplasms of the hematopoietic system, testes, kidney and brain, there are no animal data indicating that PCE causes bladder neoplasms.

Mechanistic information: Although there are no mechanistic data that provide strong evidence in support of a causal association between PCE and bladder cancer, there are studies suggesting that workers exposed to chlorinated solvents who have certain genetic polymorphisms affecting a key metabolic pathway for PCE are at increased risk of bladder cancer than those exposed to these solvents who do not have these genotypes. The metabolism of PCE takes place via two main pathways, oxidation by cytochrome P450s and conjugation with glutathione (GSH) by glutathione S-transferases (GSTs) (Guyton et al. 2014). Some metabolites of the GSH conjugation pathway, e.g., trichlorovinylglutathione (TCVG) and S-trichlorovinyl-L-cysteine (TCVC), are genotoxic (Cristofori et al. 2015). In the liver, the role of GSH is as an antioxidant and cytoprotective agent, whereas in the kidney and to some extent in the bladder epithelium, GSH functions primarily in the bioactivation and subsequent cytotoxicity of PCE (IARC 2014; Matic et al. 2014). The amount of TCVG from PCE produced in rat kidney is five-fold higher than the amount of dichlorovinylglutathione (DCVG) from TCE, indicating the importance of the GSH conjugation pathway for PCE (IARC 2014). GST enzymes play a role both in detoxification and antioxidant defense as well as bioactivation resulting in cytotoxic metabolites. Among those GST enzymes present in uroepithelium, GSTM1 plays a key role in cellular defense against free radicals whereas GSTT1 produces cytotoxic metabolites (Matic et al. 2014). Evidence from studies of workers exposed to chlorinated solvents suggested that there is effect modification of the exposure-bladder cancer relationship produced by polymorphisms in the genes for GSTM1 and GSTT1 enzymes (Simic et al. 2009; Matic et al. 2014). Chlorinated solvent-exposed workers with a GSTM1-null genotype were at a higher risk of bladder cancer compared to exposed workers with an active GSTM1 genotype and to unexposed workers with either an active or null GSTM1 genotype (Matic et al. 2014). On the other hand, chlorinated solvent-exposed workers with a GSTT1-active genotype were at a higher risk of bladder cancer compared to exposed workers with a GSTT1-null genotype and unexposed workers with either an active or null GSTT1 genotype (Matic et al. 2014). These findings suggest that lacking a fully functional GSTM1 gene and/or having a fully functional GSTT1 gene enhances the risk of bladder cancer from chlorinated solvent exposure. It is likely that those exposed to PCE who have a fully functional GSTT1 gene would have higher amounts of the genotoxic metabolites TCVG and TCVC in the kidney and bladder than those who have a null GSTT1 gene. And those exposed to PCE with a null GSTM1 gene would have a more difficult time deactivating the reactive metabolites that result from PCE metabolism via the GSH conjugate pathway.

Conclusion: The Vlaanderen et al. 2014 meta-analysis concluded that there was an increased risk of bladder cancer in the dry cleaners studies that could not be explained by confounding due to tobacco smoking. PCE was the main exposure in the dry cleaners studies and the NCI study of dry cleaning workers noted that the elevation in bladder cancer mortality risk coincided with the introduction of PCE in US dry cleaning facilities by 1960 (Blair et al. 2003). Although the meta-analysis found only a slight excess risk in the evaluation of the three studies of PCE exposed workers, this can be explained by the

limitations of these studies mentioned above. The meta-analysis is consistent with previous assessments by IARC (IARC 2014) and EPA (EPA 2012; Guyton et al. 2014) that found consistent, positive associations between PCE occupational exposure and bladder cancer. The Cape Cod, MA study of PCE-contaminated drinking water also found positive associations with bladder cancer incidence and an exposure-response trend (Aschengrau et al. 1993). At this time there are no animal data or mechanistic data that definitely support the epidemiological findings, but ATSDR believes the epidemiological studies provide sufficient evidence for causation and are consistent with the mechanistic information that certain genetic polymorphisms may enhance the production of genotoxic PCE metabolites in the bladder via the GSH conjugate pathway. Therefore, ATSDR has decided to adopt a different position from that currently held by EPA and IARC and conclude that there is **sufficient evidence for causation for PCE and bladder cancer**.

TCE

No meta-analyses have been conducted for TCE and bladder cancer. The epidemiological evidence provides only limited evidence of a positive association between TCE and bladder cancer. Of ten occupational cohort studies, six did not observe an excess risk of bladder cancer. Of the four remaining cohort studies, one study observed an exposure-response trend for cumulative exposure (Zhao et al. 2005), one study found elevated risks among those most highly exposed but the trend was not monotonic (Morgan et al. 1998), one study found elevated risks only among male workers (Hansen et al. 2013) and one study found elevated risks only among female workers (Raaschou-Nielsen et al. 2003).

The Camp Lejeune mortality studies did not find increased risks for bladder cancer (Bove et al. 2014a, b). Bladder cancer occurs mainly in older people and has a 5-year survival percentage of over 77%. Because the Camp Lejeune cohorts were relatively young at the end of follow-up, few deaths due to bladder cancer occurred.

Conclusion: ATSDR concludes that there is **below equipoise evidence for causation for TCE and bladder cancer.**

Vinyl Chloride and Benzene

Two studies evaluated benzene exposure and bladder cancer with mixed results. One study evaluated vinyl chloride exposure and bladder cancer. Given the paucity of epidemiological studies, there is insufficient information to determine whether an association exists for either vinyl chloride or benzene and bladder cancer. Therefore ATSDR concludes that for vinyl chloride and benzene there is **below equipoise evidence for causation for bladder cancer.**

Parkinson disease

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Pezzoli 2013 **Meta-analysis**	Any solvents		summary OR = 1.35 (1.09, 1.67) 16 studies summary OR = 1.58 (1.23, 2.04) for 6 higher quality studies		–
Case-Control Studies					
McDonnell 2003 Mortality 57 male cases 206 male controls 1967-1997	Any solvents	31	Any exposure to solvents: OR = 1.53 (0.81, 2.87)	<10 years: OR=1.2 (0.5, 2.7) 13 cases 10 - <20 years: OR=1.1 (0.4, 3.2) 6 cases 20 - <30 years: OR=1.3 (0.3, 5.3) 3 cases 30 + years: OR=3.6 (1.3, 10.3) 9 cases	
Goldman 2012 Prevalent (alive) Twins 99 cases 99 controls 1993-1995	(Interview &job exposure database) TCE PCE	10 5	Ever exposed: OR = 6.1 (1.2, 33) OR = 10.5 (0.97, 113)	Duration of exposure, 1-tertile difference OR=3.2 (1.1, 10) OR=3.4 (0.9, 12)	Cumulative exposure, 1-tertile difference: OR=5.2 (1.0, 26) OR=9.3 (0.8, 100)
Brouwer 2015 Mortality 402 male cases** 2098 male controls	(JEM) Aromatic solvents Chlorinated solvents 	95 13 46 40	Ever exposed (RR) Low: 0.84 (0.64, 1.10) High: 0.84 (0.45, 1.57) Ever exposed (RR) Low: 1.09 (0.76, 1.56) High: 0.93 (0.63, 1.35)	Cumulative Exposure tertiles, (RR) Aromatic Solvents # cases 1: 0.62 (0.40, 0.97) 27 2: 1.11 (0.76, 1.62) 42 3: 0.82 (0.56, 1.21) 39	Chlorinated Solvents # cases 1.00 (0.65, 1.54) 31 1.05 (0.68, 1.61) 29 0.97 (0.60, 1.55) 26
Van der Mark 2015 Incidence 444 cases 876 controls	(JEM) Aromatic solvents Chlorinated solvents 	168 14 71 37	Ever exposed (OR) Low: 0.97 (0.73, 1.29) High: 0.82 (0.43, 1.58) Ever exposed (RR) Low: 1.04 (0.74, 1.46) High: 0.86 (0.55, 1.36)	Exposure duration (yrs.) # cases Aromatic solvents: 1-7: OR=0.88 (0.61, 1.26) 57 8-24: OR=0.91 (0.62, 1.34) 54 25-67: OR=1.26 (0.80, 1.97) 71 Chlorinated solvents: 1-7: OR=0.65 (0.40, 1.06) 26 8-24: OR=1.01 (0.65, 1.57) 38 25-67: OR=1.39 (0.88, 2.20) 44	Cumulative Exposure tertiles Aromatic solvents # cases 1: OR=0.89 (0.61, 1.28) 58 2: OR=0.86 (0.58, 1.27) 52 3: OR=1.33 (0.86, 2.05) 72 Chlorinated solvents # cases 1: OR=0.74 (0.46, 1.19) 27 2: OR=1.09 (0.70, 1.69) 43 3: OR=1.15 (0.72, 1.84) 38

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Bove 2014b (Camp Lejeune Civilian worker) Mortality 4,647: Camp Lejeune 4,690: Camp Pendleton 1979-2008	VOC contaminated drinking water (modeled) vs U.S. population vs. Camp Pendleton	5	SMR = 2.19 (0.71, 5.11) HR = 3.13 (0.76, 12.86)	The cases at Lejeune had at least 18 months of exposure	Four of five deaths had above the median cumulative exposure to TCE and PCE

* Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.

** Due to small numbers of exposed female cases, the results for males are presented only in the table. (Note: The information on female exposed cases was provided in the journal article's supplementary document. For any exposure (i.e., ever low or high exposed), the number of exposed female cases and the odds ratios for aromatic solvents and chlorinated solvents were 7 cases, OR=0.74 (0.32, 1.70), and 5 cases, OR=0.48 (0.17, 1.33), respectively.

RR: Risk Ratio
OR: Odds Ratio
SMR: Standardized Mortality Ratio
HR: Hazard Ratio
95% CI: 95% Confidence Interval
JEM: Job-exposure matrix
VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)

ATSDR Assessment

The epidemiological evidence for TCE or PCE exposures and Parkinson disease is very limited because few studies have been conducted. On the other hand, there is mechanistic information based on animal studies. Therefore, ATSDR's assessment of the evidence for causation placed high weight on studies and review articles that provided mechanistic information. High weight was also given to a well-conducted twin study although the study was limited by a small number of exposed cases.

TCE and PCE

One study has evaluated TCE and PCE exposure and Parkinson disease; two studies have evaluated chlorinated solvents and aromatic solvents separately, and several studies have evaluated any solvents. A meta-analysis evaluated 16 studies that evaluated any solvents and obtained a summary OR of 1.35 that increased to 1.58 when the analysis was restricted to six higher quality studies (Pezzoli et al. 2013). The two studies of chlorinated and aromatic solvents had mixed findings (Brouwer et al. 2015 and Van der Mark et al. 2015). The key study is the Goldman et al. 2012 twin study which found high elevations in risk for both PCE and TCE with evidence of an exposure-response relationship for exposure duration and cumulative exposure. This study used rigorous methods to ensure diagnostic accuracy and to assess exposures. The twin design had the advantage of controlling for potential confounders due to genetic and shared environmental factors. A limitation was the small number of exposed cases which resulted in wide confidence intervals.

Parkinson disease mortality was evaluated in the Camp Lejeune mortality study of civilian workers and an elevated risks were observed when comparing these workers to the U.S. population (SMR=2.2, 95% CI: 0.7-5.1) and civilian workers at Camp Pendleton (RR=3.1, 95% CI: 0.8, 12.9). Although limited by the small number of deaths due to Parkinson disease, the study found that four of the five deaths occurring among the Camp Lejeune workers had above the median cumulative exposure to TCE and PCE (Bove et al. 2014b). Parkinson disease mortality could not be evaluated in the Camp Lejeune mortality study of Marines.

There have been a few case reports of Parkinson disease and Parkinsonism among TCE-exposed workers that are described in a review article of TCE and Parkinson disease by Zaheer and Slevin 2011.

Animal and mechanistic information:

TCE has been found to be a mitochondrial neurotoxin in animal studies, and mitochondrial dysfunctions in substantia nigra dopamine neurons is considered to cause the disease (Gash et al. 2008; Zaheer and Slevin 2011). Studies in rats have shown that TCE exposure causes selective loss of dopaminergic neurons in the substantia nigra pars compacta (SNpc), a pattern consistent with human pathological staging of Parkinson disease (Goldman et al. 2011). A systematic review of the toxicological and epidemiological evidence made several observations: (1) it is uncertain whether inhalation of TCE can cause similar damage since the animal studies involved oral administration of TCE; (2) it is uncertain whether TCE or its metabolites cause the damage to dopaminergic neurons in the SNpc; and (3) if a TCE metabolite is the cause of the damage, it is also possible that PCE could cause similar damage since

TCE and PCE have some common metabolites (Lock et al. 2013). The review concluded: "On balance, the convergence of toxicological and epidemiological research suggests a plausible association between TCE exposure and PD [Parkinson disease]." A recent report by the IOM echoes this conclusion: "...Parkinson disease is a neurobehavioral effect that may result from exposure to TCE and/or PCE." (IOM 2015).

Conclusion: Positive associations have been observed for TCE and PCE and Parkinson disease in a well-conducted twin study (Goldman et al. 2012). The Camp Lejeune study of civilian workers also found a positive association for Parkinson disease (Bove et al. 2014b). Because only two studies have focused on TCE exposure (Goldman et al. 2012; Bove et al. 2014b), the epidemiological evidence for causation for TCE and Parkinson disease is very limited. However, the findings from animal studies indicating a plausible mechanism for TCE exposure and Parkinson disease that is relevant to humans provides important supplemental evidence for causation. ATSDR concludes that the epidemiological evidence for causality by itself is currently too weak to achieve equipoise and above. However, given the strong supporting mechanistic evidence for TCE, ATSDR concludes that there is **equipoise and above evidence for causation for TCE and Parkinson disease.**

For PCE, the epidemiological evidence is very limited and there is no available information on a plausible mechanism as there is for TCE. However, this may change if a metabolite of TCE that is common to PCE is found to be the agent causing damage to the dopaminergic neurons. Given what is presently known, ATSDR concludes that there is **below equipoise evidence for causation for PCE and Parkinson disease.**

Kidney disease

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Cohort Studies					
Boice 2006 Mortality (nephritis & nephrosis) 7,083 1948-1999	Any TCE (job title, chemical use information)	5	Any TCE exposure: SMR=2.07 (0.67,4.82)		
Radican 2006 Incidence and Mortality (ESRD) 14,455 1973-2000	Aircraft maintenance TCE (JEM) PCE (JEM)	56 3	ESRD: HR=1.86 (1.02, 3.39) HR=0.97 (0.27, 3.52)	Person-years exposure to TCE: <2.5: HR=1.99 (1.00, 3.97) 2.5-10: HR=1.52 (0.72, 3.21) >10: HR=2.05 (1.01, 4.17) Person-years exposure to PCE: <0.5: HR=1.79 (0.39, 8.11) 0.5-2.5: 0 >2.5: HR=0.93 (0.12, 7.32)	Cumulative TCE exposure (unit-yrs) <5: HR=1.73 (0.86, 3.48) 5-25: HR=2.48 (1.20, 5.15) >25: HR=1.65 (0.82, 3.35)
Jacob 2007 Incidence 269 (cohort with glomerulonephritis) 1994-2001	TCE	6 3	Ever exposed to TCE: RR = 2.5.(0.9, 6.5) for ESRD High TCE cumulative exposure: RR=2.7 (0.7, 10.1)		
Lipworth 2011 Mortality 5,443 (TCE) 5,830 (PCE) 1960-2008	Aircraft manufacturing TCE (JEM) PCE (JEM)	40 28	Nephritis and nephrosis: SMR =1.13 (0.81, 1.54) SMR= 1.11 (0.74, 1.60)	—	
Silver 2014 Mortality 34,494 1969-2009	Microelectronics plant TCE (JEM) PCE (JEM)	56	Non-malignant chronic renal disease	—	Cumulative exposure (5 exposure-yrs) HR=1.07 (0.70, 1.63) for TCE HR=0.94 (0.47, 1.86) for PCE
Dry Cleaning Workers Studies					
Blair 2003 Mortality 5,369 1948-1993	Dry cleaning	13	SMR = 1.1 (0.6, 1.8) for chronic nephritis	—	Exposure Intensity: # cases Little/no: SMR = 0.5 (0.0, 3.8) 2 Med/high: SMR = 1.4 (0.7, 2.5) 10

Reference, type of cancer data, total # of subjects, follow-up period	Exposure^ (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Calvert 2011 Mortality 1,704 618 PCE-only 1,086 PCE-plus 1940-2004	Dry cleaning (occupation, industry surveys, personal monitoring data)		Acute glomerulonephritis/nephrotic syndrome/acute renal failure:	—	—
		4	SMR=1.62 (0.44, 4.16) All		
		2	SMR = 2.60 (0.31, 9.39) PCE only		
		2	SMR=1.18 (0.14, 4.27) PCE plus		
			Total ESRD:		
		30	SIR=1.34 (0.990, 1.91)		
		12	SIR = 1.30 (0.67, 2.26) PCE only		
		18	SIR = 1.37 (0.81, 2.17) PCE plus		
			Systemic ESRD:		
		27	SIR=1.55 (1.02, 2.25) All		
		12	SIR=1.64 (0.85, 2.86) PCE only		
		15	SIR=1.48 (0.83, 2.44) PCE plus		
			Hypertensive ESRD		
		15	SIR=1.98 (1.11, 3.27) All		
		8	SIR=2.66 (1.15, 5.23) PCE only		
		7	SIR=1.53 (0.62, 3.16) PCE plus		
Drinking Water Studies					
Bove 2014a (Camp Lejeune Marines/Navy) Mortality 154,932: Camp Lejeune 154,969: Camp Pendleton 1979-2008	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	37	SMR=0.50 (0.35, 0.68) HR=1.0 (0.63, 1.63)	—	—
Bove 2014b (Camp Lejeune Civilian worker) Mortality 4,647: Camp Lejeune 4,690: Camp Pendleton 1979-2008	VOC contaminated drinking water (modeled) vs U.S. population vs. Camp Pendleton	7	SMR=0.78 (0.34, 1.54) HR=1.23 (0.39, 3.87)	3 deaths had exposure durations of ≤6 months, and the other 4 deaths had exposure duration ≥33 months.	

* Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.
RR: Risk Ratio
OR: Odds Ratio
SMR: Standardized Mortality Ratio
SIR: Standardized Incidence Ratio
95% CI: 95% Confidence Interval
HR: Hazard Ratio
JEM: Job-exposure matrix
I: Incidence: M: mortality
VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)

ESRD: end stage renal disease. The Radican et al. 2006 study defines ESRD as chronic renal failure that has advanced to the point that either chronic dialysis or a renal transplant is necessary to survive.

Summary of EPA and IOM reviews of TCE and PCE and kidney diseases:

The EPA toxicological review of TCE (EPA 2011) concluded that high levels of TCE exposure caused proximal tubule damage and increases in various biomarkers of kidney toxicity or ESRD including β2-microglublin, total protein, NAG, and α1-microglobulin. Animal studies provide evidence that TCE exposure causes renal toxicity in the form of cytomegaly and karyomegaly of the renal tubules. Studies of TCE metabolites have demonstrated a potential role for DCVC, TCOH and TCA in TCE-induced kidney toxicity.

EPA toxicological review of PCE (EPA 2012): "Taken together, the epidemiologic studies support an association between tetrachloroethylene and chronic kidney disease, as measured by urinary excretion of renal proteins and ESRD incidence."

IOM report, Review of VA Clinical Guidance for the Health Conditions Identified by the Camp Lejeune Legislation (IOM 2015), concluded: "While there is some evidence for increased mortality from solvent-induced hypertensive end-stage renal disease (ESRD), the association between TCE and PCE and chronic kidney disease is less clear, although there does appear to be an association between exposures to high levels of these solvents and ESRD."

ATSDR Assessment

In the assessment of the evidence for causation, ATSDR placed high weight on the assessments conducted by EPA including information provided by EPA on possible mechanism. Studies that evaluated kidney disease subgroupings (e.g., ESRD) were considered to have higher utility than studies that combined all kidney diseases. Our assessment of the epidemiological evidence considered some of the viewpoints associated with Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if ≤1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding.

TCE

Five cohort studies evaluated TCE exposure and kidney diseases. Three of these cohort studies obtained relative risk estimates ≥1.9 for TCE and kidney diseases (Boice et al. 2006; Radican et al. 2006; and Jacob et al. 2007). One cohort study found an elevated risk for nephritis and nephrosis (Boice et al. 2006); another found an elevated risk for glomerulonephritis (Jacob et al. 2007); and a third found an elevated risk for ESRD (Radican et al. 2006). The other two cohort studies observed RRs of about 1.1 (Lipworth et al. 2011; Silver et al. 2014).

The Camp Lejeune mortality study of Marines did not observe an excess in all kidney diseases (HR=1.0, 95% CI: 0.63, 1.63), but the mortality study of civilian workers did observe an elevated risk in comparison with workers at Camp Pendleton (RR=1.23, 95% CI: 0.39, 3.87) (Bove et al. 2014a, b).

EPA's toxicological review of TCE noted that high occupational exposures to TCE caused damage to the proximal tubule. Several studies of TCE workers found elevated excretion of urinary proteins indicating tubule damage (EPA 2011).

Animal and mechanistic information: Evidence from animal studies indicates that TCE causes renal toxicity, and there is also evidence that TCE metabolites cause kidney toxicity.

Conclusion: Based on the evidence from epidemiological studies, occupational biomarker studies, and animal studies, ATSDR concludes that there is **equipoise and above evidence for causation for TCE and kidney diseases, in particular, ESRD.**

PCE

No meta-analyses have been conducted for PCE and kidney disease. Two cohort studies of dry cleaning workers found elevated risks for kidney disease (Blair et al. 2003; Calvert et al. 2011). One study found an elevated risk for chronic nephritis among workers with medium to high exposures (Blair et al. 2003). The other dry cleaning worker study found elevated risks for the combined outcome, acute glomerulonephritis, nephrotic syndrome, and acute renal failure, systemic ESRD and hypertensive ESRD among workers exposed to only PCE (Calvert et al. 2011). Three cohort studies evaluated industrial workers exposed to PCE and kidney diseases. PCE exposures in these studies were likely much lower than in the dry cleaning studies. Two of the cohort studies of PCE workers did not observe elevated risks for kidney disease (Radican et al. 2006; Silver et al. 2014) and another study observed a relative risk of 1.1 for nephritis and nephrosis (Lipworth et al. 2011). The findings in these three cohort studies may be due to low PCE exposures.

EPA's toxicological review of PCE noted that occupational exposures to PCE caused damage to the proximal tubule as measured by urinary excretion of renal proteins (EPA 2012).

Animal and mechanistic information: Evidence from animal studies indicates that PCE causes renal toxicity in the form of tubular toxicity. This effect is potentially caused by PCE metabolites via the GSH conjugation pathway.

Conclusion: The biomarker, animal and mechanistic evidence is similar in strength for PCE and TCE. However, the epidemiological evidence for PCE and kidney diseases is somewhat weaker than for TCE. Although the two dry cleaning worker cohort studies observed elevated risks, two cohort studies of industrial workers exposed to PCE found no elevation in risk. It is likely that the discrepancy in the epidemiological results is due to much lower PCE exposures in the industrial cohorts compared to the dry cleaning cohorts. Therefore ATSDR considers the dry cleaning studies to be more informative than the industrial worker studies in evaluating the effects of PCE exposure, and views the evidence for causality to be at least equipoise. ATSDR concludes that there is **equipoise and above evidence for causation for PCE and kidney diseases, in particular, ESRD.**

Esophageal Cancer

Reference, type of cancer data, total # of subjects, follow-up period	Exposure[*] (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Cohort Studies					
Raaschou-Nielsen 2003 Incidence Adenocarcinomas[¥] 40,049 1964-1997	TCE (Job title, plant air monitoring, Urine TCA)	23 10	Any exposure: SIR=1.8 (1.2, 2.7) SIR=1.7 (0.8, 3.0) 20 year lag	Duration of employment (yrs.) <1: SIR=1.7 (0.6, 3.6) 6 cases 1-4.9: SIR=1.9 (0.9, 3.6) 9 cases >5: SIR=1.9 (0.8, 3.7) 8 cases	Higher exposed workers, exposure lag period (years): 0-9: no exposed cases 10-19: SIR=2.3 (0.9, 5.0) 6 cases ≥20: SIR=1.6 (0.6, 3.2) 7 cases
Boice 2006[€] Mortality 7,083 1948-1999	Any TCE (job title, chemical use information)	3	SMR=0.88 (0.18, 2.58)		
Radican 2008 Mortality 14,455 1953-2000	Aircraft maintenance TCE (JEM)	17 15 2	Any TCE exposure: HR=1.88 (0.61, 5.79) Men: HR=1.66 (0.48, 5.74) Women: HR=2.81 (0.25, 31.1)	Cumulative exposure score (unit-yr) Men only: # cases 0-5: HR=1.84 (0.48, 7.14) 7 5-25: HR=1.33 (0.27, 6.59) 3 >25: HR=1.67 (0.40, 7.00) 5	Intensity (Men only) (HR) # cases Low, intermittent: 1.92 (0.55, 6.73) 13 Low, continuous: 0.98 (0.22, 4.41) 4 Peak, infrequent: 2.15 (0.43, 10.7) 3 Peak, frequent: 1.59 (0.40, 6.41) 6
Lipworth 2011 Mortality 5,443 (TCE) 5,830 (PCE) 1960-2008	Aircraft manufacturing TCE (JEM) PCE (JEM)	19 24	SMR=0.65 (0.39, 1.01) SMR=1.13 (0.72, 1.68)	Years exposed to TCE: # cases <1: RR=0.53 (0.22, 1.24) 7 1-4 RR=0.62 (0.23, 1.63) 5 ≥5 RR=0.77 (0.32, 1.86) 7	Years exposed to PCE: # cases <1: RR=2.30 (1.14, 4.66) 11 1-4 RR=1.30 (0.56, 3.02) 7 ≥5 RR=0.66 (0.22, 1.96) 4
Hansen 2013 Incidence 3,776 male workers Finland:1967-2004 Sweden: 1958-2003 Denmark: 1968-2008	TCE (Urine TCA)	11	Any exposure: Men: SIR=1.30 (0.65, 2.32) (1 case among women)	Lagtime (years) # cases 10: SIR=1.20 (0.60, 2.14) 11 20: SIR=1.46 (0.67, 2.78) 9	Urine TCA (mg/L) Ref: <5 5-25: RR=0.48 (0.14, 1.60) 4 cases >25 0
Carreón 2014 Mortality 1,874 1960-2007	Vinyl chloride	4	Any exposure: SMR=1.12 (0.30, 2.86)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure[a] (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Linet 2015 Mortality 73,789 exposed 35,504 unexposed 1972-1999	Benzene	70	Any exposure: RR=1.6 (1.0, 2.5)		
Case-Control Study					
Santibañez 2008 Incidence 185 cases 285 controls 1995-1999	JEM Chlorinated solvents Aromatic solvents		Exposure level: All esophageal cases # cases Squamous cell # cases Adenocarcinoma # cases Low: OR=1.05 (0.15, 7.17) 2 0 OR=4.92 (0.69, 34.7) 2 High: OR=1.76 (0.40, 7.74) 6 OR=2.18 (0.41, 11.6) 5 OR=3.03 (0.28, 32.2) 1 Low: OR=1.33 (0.50, 3.53) 11 OR=1.63 (0.49, 5.43) 8 OR=2.27 (0.53, 9.63) 3 High: OR=0.38 (0.06, 2.22) 2 0 OR=3.07 (0.53, 17.6) 2		
Dry Cleaning Worker Studies					
Vaughan 1997 Incidence 109 squamous cell 295 adenocarcinoma 724 controls 1983-1990	Dry cleaning	2 2	OR=3.6 (0.5, 27.0) Squamous cell (both cases had an exposure duration of 1-9 years and probable exposure to PCE) OR=1.1 (0.2, 5.7) Adenocarcinoma (1 case each had exposure duration of 1-9 and ≥10 years. One case had probable exposure to PCE.)		
Blair 2003 Mortality 5,369 1948-1993	Dry cleaning	26	SMR=2.2 (1.5, 3.3)		Exposure Level (SMR): # cases Little/no: 2.1 (0.9, 4.4) 7 Medium/high: 2.2 (1.2, 3.5) 16
Calvert 2011 Mortality 1,704 618 PCE-only 1,086 PCE-plus 1940-2004	Dry cleaning (occupation, industry surveys, personal monitoring data)	16 6 10	SMR=2.44 (1.40, 3.97) All SMR=2.68 (0.98, 5.83) PCE only SMR=2.32 (1.11, 4.27) PCE plus	≥20 years since 1st employment, duration of employment (yrs) <5: SMR=2.16 (0.85, 4.54) 5 cases >5: SMR=4.78 (2.68, 7.91) 11 cases	
Selden 2011 Incidence 9,440 1985-2006	Dry Cleaning and Laundry Workers: (plant survey, work history)	0 5	Any exposure Men: — Women: SIR=1.33 (0.43, 3.10)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Drinking Water Studies					
Bove 2014a (Camp Lejeune Marines/Navy) Mortality 154,932: Camp Lejeune 154,969: Camp Pendleton 1979-2008	VOC contaminated drinking water (modeled) vs U.S. population vs. Camp Pendleton	35	SMR=0.85 (0.59, 1.18) HR=1.43 (0.85, 2.38)	Duration of exposure (months) 1-3: OR=0.3 (0.0, 2.5) 1 case 4-6: OR=1.9 (0.6, 5.8) 4 cases 7-12: OR=1.5 (0.6, 3.9) 6 cases >12: OR=0.7 (0.3, 1.5) 10 cases	
Bove 2014b (Camp Lejeune Civilian Workers) Mortality 4,647: Camp Lejeune 4,690: Camp Pendleton 1979-2008	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	4	SMR=0.64 (0.18, 1.65) HR=0.58 (0.15, 2.22)		

* Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.

♭ There were no female cases of adenocarcinomas, so the results in the table are for male workers.

© This study overlaps considerably with Zhao et al. 2005. Although the Zhao study evaluated incidence, an important consideration given the low survivability of esophageal cancer, the study unfortunately combined esophageal and stomach cancers so it is not include in the table.

Urine TCA: urine levels of trichloroacetic acid, a metabolite of TCE.

RR: Risk Ratio

OR: Odds Ratio

SMR: Standardized Mortality Ratio

SIR: Standardized Incidence Ratio

95% CI: 95% Confidence Interval

HR: Hazard Ratio

JEM: Job-exposure matrix

I: Incidence; M: mortality

VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)

Note: Lynge et al. 2006 is omitted because a majority of the cases were unclassifiable on exposure status. If all the unclassifiable were exposed, then RR=1.19 (0.67, 2.12). If all the unclassifiable were unexposed, then RR=0.66 (0.30, 1.45). For those that could be classified as dry cleaner workers, RR=0.76 (0.34, 1.69) based on 8 exposed cases. When the analysis was restricted to Denmark and Norway with no unclassifiable cases, the RR=0.91 (0.38, 2.20) among dry cleaning workers.
Note: Christensen et al. 2013 is omitted because there were no PCE-exposed cases and only one TCE-exposed case.

ATSDR Assessment

ATSDR's assessment of the epidemiological evidence considered some of the viewpoints associated with Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if ≤1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding.

TCE

No meta-analyses were conducted of TCE exposure and esophageal cancer. Five cohort studies evaluated TCE exposed workers and esophageal cancer. None of these studies could adjust for smoking or alcohol consumption although internal analyses were likely unaffected by confounding due to these risk factors. Three cohort studies of TCE exposed workers and esophageal cancer found elevated risks (Raaschou-Nielsen et al. 2003, Radican et al. 2008, and Hansen et al. 2013). Relative risks for any exposure to TCE in these three studies ranged from 1.3 to 1.8 (an RR of 2.8 was found for female workers in the Radican et al. study based on 2 esophageal cancer deaths). A monotonic exposure-response trend for duration of employment was found in the Raaschou-Nielsen et al. study. A non-monotonic trend for cumulative exposure was observed in the Radican et al. 2008 study with the highest RRs occurring for the lowest category of cumulative exposure and for low intermittent and peak infrequent exposures. The Hansen et al. 2013 study did not observe an exposure-response trend for urine TCA but the analysis was limited by small numbers of exposed cases. Two cohort studies did not find an excess risk (Boice et al. 2006; Lipworth et al. 2011). One of these studies had only three exposed esophageal cancer deaths (Boice et al. 2006). Healthy worker effect bias was evident in the other study with SMRs for all cancers and for esophageal cancer of 0.92 (95% CI: 0.86, 0.97) and 0.65 (95% CI: 0.39, 1.01), respectively (Lipworth et al. 2011).

An elevated HR was observed in the Camp Lejeune mortality study of Marines and Navy personnel (Bove et al. 2014a) but not in the study of civilian workers (Bove et al. 2014b). There were only four esophageal cancer deaths among the civilian workers at Camp Lejeune.

Conclusion: The two cohort studies that did not observe an elevated risk had serious limitations including small numbers of exposed cases (Boice et al. 2006) and healthy worker effect bias (Lipworth et al. 2011). Of the three cohort studies that did observe elevated risks, only one study observed higher risks associated with higher or longer exposures (Raaschou-Nielsen et al. 2003). ATSDR concludes that the epidemiological evidence for causality by itself is currently too weak to achieve equipoise and above. Given the lack of supporting animal and/or mechanistic evidence, ATSDR concludes that there is **below equipoise evidence for causation for TCE and esophageal cancer**.

PCE

No meta-analyses were conducted of PCE exposure and esophageal cancer. Five dry cleaning worker studies and one study of aircraft manufacturing workers evaluated PCE exposure and esophageal cancer. None of these studies could adjust for smoking or alcohol consumption although internal analyses were likely unaffected by confounding due to these risk factors.

Among the five dry cleaning studies, one did not observe an excess risk, but this study was seriously limited because a majority of the esophageal cancer cases were unclassifiable on exposure status (Lynge et al. 2006). One study observed an elevated odds ratio for squamous cell esophageal cancer but was based on only 2 exposed cases (OR=3.6, 95% CI: 0.5, 27) (Vaughan et al. 1997). One study had no exposed male cases and an SIR of 1.33 (95% CI: 0.43, 3.10) based on five exposed female cases (Selden and Ahlborg 2011). Two studies observed elevated risks and were also able to evaluate exposure-response trends (Blair et al. 2003; Calvert et al. 2011). In the Blair et al. 2003 study, an elevated risk (SMR=2.2, 95% CI: 1.2, 3.5) among medium to high exposed workers was only slightly higher than the risk for those with little or no exposure (SMR=2.1, 95% CI: 0.9, 4.4). On the other hand, the Calvert et al. 2011 study observed an elevated risk for workers exposed to PCE only (SMR=2.68, 95% CI: 0.98, 5.83) and a monotonic exposure-response trend for employment duration.

The cohort study of aircraft manufacturing workers obtained an SMR of 1.13 (95% CI: 0.72, 1.68). In this study, the risk decreased with increasing duration of exposure so that an RR of 0.66 (95% CI: 0.22, 1.96) was observed for those with five or more years of exposure (Lipworth et al. 2011). However, exposures to PCE in this study were likely much lower than in the dry cleaning worker studies.

Conclusion: Although several of the studies observed elevated risks, some were based on small numbers of exposed cases and only one study observed an exposure-response trend. ATSDR concludes that the epidemiological evidence for causality by itself is currently too weak to achieve equipoise and above. Given the lack of supporting animal and/or mechanistic evidence, ATSDR concludes that there is **below equipoise evidence for causation for PCE and esophageal cancer**.

Benzene and vinyl chloride

One cohort study evaluated benzene and observed a RR of 1.6 (95% CI: 1.0, 2.5). One cohort study evaluated vinyl chloride and observed an SMR of 1.12 (95% CI: 0.30, 2.86). Because only one study each evaluated benzene and vinyl chloride, there was insufficient information to determine whether an association exists between these two chemicals and esophageal cancer. Therefore ATSDR concludes that there is **below equipoise evidence for causation for benzene and vinyl chloride and esophageal cancer**.

Chlorinated/Aromatic Solvents

One case-control study evaluated chlorinated and aromatic solvents as a group. For high level exposures to chlorinated solvents, the OR for all esophageal cases was 1.76 (95% CI: 0.40, 7.74). For high level

exposures to aromatic solvents, an elevated OR was observed only for adenocarcinoma (OR=3.07, 95% CI: 0.53, 17.6). This study was limited by small numbers of exposed cases, the collection of information on just the two longest occupations of each individual, and the use of a generic JEM.

Rectal Cancer

Reference, type of cancer data, total # of subjects, follow-up period	Exposure[a] (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Cohort Studies					
Anttila 1995 Incidence 3,089 TCE 1967-1992	TCE (urine TCA)	12	Any exposure: SIR=1.71 (0.88, 2.98)		Urine TCA (µmol/L): <100 SIR=2.34 (1.07, 4.44) 9 cases 100 + SIR=0.85 (0.10, 3.07) 2 cases
Morgan 1998 Mortality 4,733 1950-1993	Aerospace TCE subcohort	6	Any exposure to TCE: SMR=1.06 (0.39, 2.31)		Cumulative Exposure (SMR) # cases Low: 0.49 (0.01, 2.74) 1 High: 1.38 (0.45, 3.21) 5
Raaschou-Nielsen 2003 Incidence 40,049 1964-1997	TCE (job title, plant air monitoring & Urine TCA data)	128 15	Any exposure: Men, SIR=1.1 (1.0, 1.4) Women, SIR=1.1 (0.6, 1.8)		
Chang 2003 Mortality 86,868 1985-1997	Chlorinated organic solvents	2 13	Any exposure: Men: SMR=0.73 (0.08, 2.65) Women: SMR=1.67 (0.89, 2.85)	Duration of Employment (years): women only[e] ≤1: SMR=1.81 9 cases 1-≤5: SMR=1.01 2 cases >5: SMR=2.50 2 cases	
Zhao 2005 Incidence 6,044 1950-2001	Aerospace TCE (JEM)	28 13			Cumulative exposure (RR) # cases[f] Medium: 0.93 (0.58, 1.50) 28 High: 0.92 (0.49, 1.72) 13
Radican 2008 Mortality 14,455 1953-2000	Aircraft maintenance TCE (JEM)	9 8	Any exposure: HR=0.65 (0.22, 1.93) Male: HR=0.64 (0.19, 2.12)		
Lipworth 2011 Mortality 5,443 (TCE) 5,830 (PCE) 1960-2008	Aircraft manufacturing TCE (JEM) PCE (JEM)	20 10	SMR=0.96 (0.59, 1.49) SMR=0.82 (0.39, 1.50)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure[x] (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Hansen 2013 Incidence 5,553 Finland:1967-2004 Sweden: 1958-2003 Denmark: 1968-2008	TCE (urine TCA was used to identify workers ever exposed to TCE)	 43 33 10	Any exposure: All: SIR=1.06 (0.78, 1.43) Men: SIR=1.11 (0.76, 1.56) Women: SIR=0.94 (0.45, 1.73)		
Linet 2015 Mortality 73,789 exposed 35,504 unexposed 1972-1999	Benzene	79[z]	Any exposure: RR=1.5 (1.0, 2.3)		
Buhagen 2016 Incidence 997 males 1960-2010	Train maintenance TCE (union employment list)	13	SIR=1.2 (0.7, 2.0)		
Case-Control Study					
Christensen 2013 Incidence 248 cases 533 controls	TCE PCE[y]	13 3 4	Any: OR=1.8 (0.8, 4.0) Substantial: OR=0.7 (0.2, 2.6) Any: OR=2.1 (0.5, 8.7)		
Dry Cleaning Workers Studies					
Blair 2003 Mortality 5,369 1948-1993	Dry cleaning	15	Any exposure: SMR=1.3 (0.7, 2.2)		
Calvert 2011 Mortality 1,704 618 PCE-only 1,086 PCE-plus 1940-2004	Dry cleaning (occupation, industry surveys, personal monitoring data)	7 0 7	All: SMR=1.26 (0.51, 2.59) PCE only: SMR=0 PCE plus: SMR=1.81 (0.73, 3.74)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Selden 2011 Incidence 9,440 1985-2006	Dry Cleaning & Laundry Workers (plant survey, work history)	38	SIR=0.83 (0.59, 1.14)		
Drinking Water Studies					
Paulu 1999 Incidence 311 colo-rectal cases 1,158 controls 1983-1986	PCE contaminated drinking water (modeled)	§	Ever exposed: (rectal cancer only) OR=2.6 (0.8, 6.7) for 11 year latency OR=3.1 (0.7, 10.9) for 13 year latency		
Bove 2014 (Camp Lejeune Marines/Navy) Mortality 154,932: Camp Lejeune 154,969: Camp Pendleton 1979-2008	VOC contaminated drinking water (modeled) vs U.S. population vs. Camp Pendleton	24	SMR=0.81 (0.52, 1.21) HR=1.60 (0.83, 3.07)	Duration of exposure (months) 1-3 OR=1.0 (0.2, 4.8) 2 cases 4-6 OR=0.7 (0.1, 5.9) 1 case 7-12 OR=0.8 (0.2, 3.6) 2 cases >12 OR=1.1 (0.4, 2.6) 10 cases	
Bove 2014 (Camp Lejeune Civilian Workers) Mortality 4,647: Camp Lejeune 4,690: Camp Pendleton 1979-2008	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	4	SMR=1.06 (0.29, 2.72) HR=1.65 (0.36, 7.44)		

* Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.

[e] Although not stated in the text, the analysis of duration of employment appears to be limited to women. Among chlorinated solvent exposed workers, there were only 2 rectal cancer deaths among men and 13 rectal cancer deaths among women. The text stated that the analysis of duration was limited to cancers with at least 3 deaths, and there are 13 rectal cancer deaths in the duration analysis, so it appears that this analysis was limited to women. No confidence intervals were provided of duration of employment.

[£] The study combined colon and rectal cancers and did not evaluate rectal cancers separately.

[¥] The Christensen et al. 2013 study had 3 cases of rectal cancer with "substantial exposure" to TCE, and only 1 case with "substantial exposure" to PCE.

[§] The study provided only the number of cases for colon and rectal cancers combined. Most of the colon-rectal cancer cases were colon cancer.

RR: Risk Ratio

OR: Odds Ratio

SMR: Standardized Mortality Ratio

SIR: Standardized Incidence Ratio

95% CI: 95% Confidence Interval

sRR: Summary Risk Ratio

HR: Hazard Ratio

JEM: Job-exposure matrix

I: Incidence; M: mortality

VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)

Urine TCA: urine levels of trichloroacetic acid, a metabolite of TCE.

ATSDR Assessment

ATSDR's assessment of the epidemiological evidence considered some of the viewpoints associated with Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if ≤1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding.

TCE

No meta-analyses have been conducted of TCE and rectal cancer. Eight cohort studies evaluated worker exposure to TCE and rectal cancer. Three of the cohort studies did not find an elevated risk (Zhao et al. 2005, Radican et al. 2008, Lipworth et al. 2011). Three cohort studies found risks near the null: SMR=1.06, 95% CI: 0.39, 2.31 (Morgan et al. 1998), SIR=1.06, 95% CI: 0.78, 1.43 (Hansen et al. 2013), and SIR=1.1, 95% CI: 1.0, 1.4 for men and SIR=1.1, 95% CI: 0.6, 1.8 for women. Elevated risks were observed in two studies: an SIR of 1.2 (95% CI: 0.7, 2.0) (Buhagen et al. 2016), and an SIR of 1.71 (95% CI: 0.88, 2.98) (Anttila et al. 1995).

Three of these cohort studies evaluated exposure-response trends. One study found no elevation in risk (Zhao et al. 2005). One study observed an elevated risk among those with lower urine TCA levels (SIR=2.34, 95% CI: 1.07, 4.44) but not among those with higher urine TCA levels (SIR=0.85, 95% CI: 0.10, 3.07, based on 2 cases) (Anttila et al. 1995). And one study observed an elevated risk in the high cumulative exposure category (SMR=1.38, 95% CI: 0.45, 3.21) but had only 1 case in the low cumulative exposure category (SMR=0.49, 95% CI: 0.01, 2.74).

One case-control study found an elevated risk for "any exposure" (OR=1.8, 95% CI: 0.8, 4.0) but not for "substantial" exposure (OR=0.7, 95% CI: 0.2, 2.6), although the study was limited by a small number of exposed cases who had "substantial" exposure to TCE (Christensen et al. 2013). Both Camp Lejeune mortality studies observed an excess rectal cancer when the Camp Lejeune cohorts were compared to Camp Pendleton (Bove et al. 2014a, b).

Conclusion: Based on the mixed findings in the epidemiological studies, ATSDR concludes that there is **below equipoise evidence for causation for TCE and rectal cancer.**

PCE

No meta-analyses have been conducted of PCE and rectal cancer. Three cohort studies evaluated dry cleaning workers. Blair et al. 2003 observed an SMR of 1.3 (95% CI: 0.7, 2.2) for any exposure. Calvert

et al. 2011 had no rectal cancer deaths in the group of workers exposed only to PCE but did observe an elevated risk (SMR=1.81, 95% CI: 0.73, 3.74) for workers who possibly worked with other solvents in addition to PCE. The Selden et al. 2011 study found no elevated risk. None of these studies evaluated exposure-response trends.

A cohort study of aircraft manufacturing workers (Lipworth et al. 2011) did not find an elevated risk but exposures to PCE in this study were low compared to the dry cleaning studies. A case-control study observed an elevated risk for any PCE exposure (OR=2.1, 95% CI: 0.5, 8.7) based on four exposed cases but had only one case with "substantial" PCE exposure (Christensen et al. 2013).

The Cape Cod drinking water study evaluated colorectal cancers as a group but did report findings for rectal cancer in the text of the article (Paulu et al. 1999). The study found an elevated risk for those ever exposed to PCE-contaminated drinking water (OR=2.6, 95% CI: 0.8, 6.7, for 11-year latency period, and OR=3.1, 95% CI: 0.7, 10.9, for 13-year latency period). The number of rectal cancers evaluated were not provided in the text, but the confidence intervals for the odds ratio estimates were extremely wide indicating a small number of exposed cases.

Conclusion: The epidemiological evidence for an association between PCE exposure and rectal cancer is weak. The findings of several of the studies were based on small numbers of exposed cases. Of the three studies with ≥10 exposed cases, the findings were conflicting (Blair et al. 2003, Selden et al. 2011, and Lipworth et al. 2011). Because of the weak epidemiological evidence, ATSDR concludes that there is **below equipoise evidence for causation for PCE and rectal cancer**.

Brain (Central Nervous System) Cancer

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Boffetta 2003 **Meta-analysis**	Vinyl chloride	68	SMR=1.26 (0.98, 1.62) based on 5 studies		
Cohort Studies					
Anttila 1995 Incidence 3,089 TCE 849 PCE 1967-1992	TCE (Urine TCA) PCE (blood PCE)	9 2	SIR=1.09 (0.50, 2.07) SIR=1.15 (0.14, 4.15)		Urine TCA (µmol/L): # cases <100 SIR=1.52 (0.61, 3.13) 7 100 + SIR=0.76 (0.09, 2.74) 2
Morgan 1998 Mortality 4,733 1950-1993	Aerospace TCE subcohort	4	Any exposure: SMR=0.55 (0.15, 1.40)		Cumulative exposure # cases Low: SMR=0.73 (0.09, 2.64) 2 High: SMR=0.44 (0.05, 1.58) 2
Blair 2003 Mortality 5,369 1948-1993	Dry cleaning	5	Any Exposure: SMR=0.6 (0.2, 1.4)		
Raaschou-Nielsen 2003 Incidence 40,049 1964-1997	TCE (job title, plant air monitoring, Urine TCA data)	85 19	Any TCE exposure: Men, SIR=1.0 (0.8, 1.2) Women, SIR=1.1 (0.7, 1.7)		
Zhao 2005 Mortality 6,044 mortality[x] 1950-2001	Aerospace TCE (JEM)				Cumulative exposure (RR) # cases Medium: 0.42 (0.12, 1.50) 3 High: 0.83 (0.23, 3.08) 3
Chang 2005 Incidence 1979-1997 86,868	Electronics Factory, chlorinated organic solvents	2 15	Any exposure: Men: SIR=0.40 (0.05, 1.46) Women: SIR=0.97 (0.54, 1.61)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Radican 2008[¶] Mortality 10,730 men 1953-2000	Aircraft maintenance TCE (JEM)	17	Any exposure: Men: HR=1.26 (0.43, 3.75)	Cumulative exposure score (unit-yr) 0-5: HR=1.46 (0.44, 4.86) 8 cases 5-25: HR=1.74 (0.49, 6.16) 6 cases >25: HR=0.66 (0.15, 2.95) 3 cases	Exposure intensity (HR) # cases Low, intermittent: 0.92 (0.28, 2.98) 9 Low, continuous: 1.37 (0.42, 4.46) 9 Peak, infrequent: 3.00 (0.85, 10.6) 6 Peak, frequent: 0.88 (0.24, 3.26) 5
Lipworth 2011 Mortality 5,443 (TCE) 5,830 (PCE) 1960-2008	Aircraft manufacturing TCE (JEM) PCE (JEM)	20 16	SMR=0.85 (0.52, 1.32) SMR=1.00 (0.57, 1.63)		
Selden 2011 Incidence 9,440 1985-2006	Dry Cleaning and Laundry Workers: (plant survey, work history)	36 9 27	Any exposure All: SIR=0.99 (0.69, 1.37) Men: SIR=0.97 (0.44, 1.83) Women: SIR=1.00 (0.66, 1.45)		
Hansen 2013 Incidence 5,553 Finland:1967-2004 Sweden: 1958-2003 Denmark: 1968-2008	TCE (Urine TCA was used to identify workers ever exposed to TCE)	24 16 8	Any Exposure: All: SIR=0.79 (0.51, 1.17) Men: SIR=0.82 (0.47, 1.34) Women: SIR=0.73 (0.31, 1.43)		
Silver 2014 Mortality 34,494 1969-2009	Microelectronics plant TCE (JEM) PCE (JEM)	55			Cumulative exposure (5 exposure-yr) HR=0.01 (0.00, 24.6) HR=0.56 (0.12, 2.65)
Linet 2015 Incidence 73,789 exposed 35,504 unexposed 1972-1999	Benzene	18	Any exposure: RR=0.8 (0.4, 1.6)		
Buhagen 2016 Incidence 997 males 1960-2010	Train maintenance TCE (union employment list)	4	SIR=0.7 (0.3, 1.9)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Case-Control Studies					
Neta 2012 Incidence 489 glioma cases 197 meningioma cases 799 controls 1994-1998	(JEM) TCE (probable exposure)	11 8 3 6	Glioma OR=0.5 (0.3, 1.1) All OR=0.4 (0.2, 1.0) Men OR=1.0 (0.2, 4.3) Women Meningioma OR=1.5 (0.4, 6.3)	ORs for exposure duration for gliomas and PCE or TCE were ≤ 1.0. Duration of exposure for meningioma was not evaluated.	ORs for cumulative exposure for gliomas and PCE or TCE were ≤ 1.0. Cumulative exposure for meningioma was not evaluated.
	PCE (probable exposure)	9 6 3 3	Glioma OR=0.7 (0.3, 1.6) All OR=1.2 (0.4, 3.8) Men OR=0.5 (0.1, 1.7) Women Meningioma OR=0.3 (0.1, 1.7)		
Ruder 2013 Incidence 798 glioma cases 1,175 controls 1995-1997	TCE	302 221 81	OR=0.74 (0.61, 0.90) All OR=0.88 (0.69, 1.12) Men OR=0.57 (0.42, 0.79) Women		ORs for cumulative exposure to PCE or TCE were <1.0
	PCE	299 216 83	OR=0.75 (0.62, 0.91) All OR=0.81 (0.64, 1.04) Men OR=0.66 (0.48, 0.91) Women		
Drinking Water Studies					
Paulu 1999 Incidence 36 cases 703 controls 1983-1986	PCE contaminated drinking water (modeled)	3	OR=0.6 (0.1, 1.7) OR=1.0 (0.2, 2.9) 5 year latency		
Bove 2014 (Camp Lejeune Marines/Navy) Mortality 154,932: Camp Lejeune 154,969: Camp Pendleton 1979-2008	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	74	SMR=0.83 (0.65, 1.04) HR=0.93 (0.67, 1.30)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Bove 2014 (Camp Lejeune Civilian Workers) Mortality 4,647: Camp Lejeune 4,690: Camp Pendleton 1979-2008	VOC contaminated drinking water vs U.S. population vs. Camp Pendleton	7	SMR=1.05 (0.42, 2.16) HR=0.65 (0.21, 2.04)		

* Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.

¥ The findings for brain cancer incidence were based on 2 medium exposed and 1 high exposed case with RRs of 0.5.

¶ There were no brain cancer deaths among female workers.

RR: Risk Ratio

OR: Odds Ratio

SMR: Standardized Mortality Ratio

SIR: Standardized Incidence Ratio

95% CI: 95% Confidence Interval

sRR: Summary Risk Ratio

HR: Hazard Ratio

JEM: Job-exposure matrix

I: Incidence; M: mortality

VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)

Urine TCA: urine levels of trichloroacetic acid, a metabolite of TCE.

ATSDR Assessment

ATSDR's assessment of the epidemiological evidence considered some of the viewpoints associated with Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if ≤1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding. Studies that evaluated brain cancer sub-groupings were considered to have higher utility than studies that did not. A meta-analysis of vinyl chloride and brain cancer was given high weight.

TCE

No meta-analyses have been conducted of TCE and brain cancer. Eleven studies evaluated TCE worker exposure and brain cancer, nine cohort studies and two case-control studies. Of these, six studies were based on eleven cases or fewer resulting in extremely wide confidence intervals. The largest study, a case-control study of glioma, found no elevated risk (Ruder et al. 2013). Another case-control study found no elevated risk for glioma but an elevated risk for meningioma (OR=1.5, 95% CI: 0.4, 6.3) based on six exposed cases (Neta et al. 2012). Six of the nine cohort studies did not observe an elevated risk (Morgan et al. 1995, Zhao et al. 2005, Lipworth et al. 2011, Hansen et al. 2013, Silver et al. 2014 and Buhagen et al. 2016). Of the three cohort studies that did observe an elevated risk, two observed SIRs ≤1.1 (Antilla et al. 1995; female workers only in the Raaschou-Nielsen et al. 2003 study). The highest elevation in risk was observed in the Radican et al. 2008 cohort study (RR=1.26, 95% CI: 0.43, 3.75). Both Camp Lejeune mortality studies did not observe an elevated risk (Bove et al. 2014a, b).

Conclusion: The evidence from the epidemiological studies could be interpreted as supporting a position that TCE does not cause brain cancer. However, because a majority of the studies were based on small numbers of exposed cases, ATSDR concludes that the evidence is too weak to conclude that TCE does not cause brain cancer. ATSDR's conclusion is that there is insufficient evidence to determine whether an association exists for TCE and brain cancer. Therefore, there is **below equipoise evidence for causation for TCE and brain cancer.**

PCE

No meta-analyses have been conducted of PCE and brain cancer. The epidemiological evidence for PCE and brain cancer is weaker than that for TCE. Of the six studies that evaluated PCE worker exposure and brain cancer, four observed no elevated risk including a large case-control study. One case-control study observed an elevated risk for glioma among male workers probably exposed to PCE (OR = 1.2, 95% CI: 0.4, 3.8) based on six exposed cases but not for meningioma (Neta et al. 2012). A cohort study

based on 2 exposed cases found an SIR of 1.15 (95% CI: 0.14, 4.15) (Antilla et al. 1995). Half of the six studies had six or less exposed cases.

No excess risk for brain cancer was observed in the Cape Cod drinking water study (Paulu et al. 1999).

Animal and mechanistic information: PCE has been shown to cause brain gliomas in both sexes in rodent studies (EPA 2012).

Conclusion: The evidence from the epidemiological studies could be interpreted as supporting a position that PCE does not cause brain cancer. However, because a majority of the studies were based on small numbers of exposed cases, ATSDR concludes that the evidence is too weak to conclude that PCE does not cause brain cancer. In addition, the positive findings in rodents provide evidence against a conclusion that PCE does not cause brain cancer. Therefore ATSDR concludes that there is insufficient evidence to determine whether an association exists for PCE and brain cancer. Therefore, there is **below equipoise evidence for causation for PCE and brain cancer.**

Vinyl Chloride

A meta-analysis obtained a summary SMR of 1.26 (95% CI: 0.98, 1.62) based on 5 studies with a total of 68 exposed brain cancer deaths. The authors stated that the excess in brain cancer deaths was mainly due to the North American multicenter study which contributed 36 of the 68 deaths. Fifteen of these deaths came from one polymer production plant in Louisville, KY (Lewis et al. 2003a). When this plant was analyzed separately, the SMR for brain cancer was 2.29 (95% CI: 1.29, 3.81), but the SMR for the rest of the plants in the multicenter study was 1.12 (95% CI: 0.69, 1.71). This indicated that the excess mortality in the North American multicenter study, and the meta-analysis itself, was primarily due to the Louisville plant. When the brain cancer deaths at the Louisville plant were reviewed, no association was found for vinyl chloride exposure (Lewis et al. 2003b). Based on these analyses, ATSDR concludes that there is **below equipoise evidence for causation for vinyl chloride and brain cancer.**

Benzene

One cohort study that evaluated brain cancer incidence and benzene exposure observed no excess. Since only one study has been conducted, ATSDR concludes that there is insufficient evidence to determine whether an association exists for benzene and brain cancer. Therefore, there is **below equipoise evidence for causation for benzene and brain cancer.**

Scleroderma/Systemic Sclerosis

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Cooper 2009 **Meta-analysis** (EPA)	TCE	 26 41	Pooled OR: Men: 2.46 (1.13, 5.38) 2 studies Women: 1.22 (0.58, 2.57) 3 studies		
Zhao 2016 **Meta-analysis**	TCE PCE Benzene	TCE PCE Benzene	Summary OR=2.07 (1.34, 3.17) 5 studies Summary OR=2.03 (0.44, 9.27) 3 studies Summary OR=1.02 (0.59, 1.75) 3 studies		
Case-Control Studies					
Nietert 1998[¶,§] 178 cases 200 controls 1995-1997	(JEM) TCE Benzene		Men (OR) # cases Women # cases Any exposure[‡]: 2.0 (0.8, 4.9) 19 0.7 (0.4, 1.3) 27 Max intensity: 3.3 (1.0, 10.3) 11 0.9 (0.3, 2.3) 8 Cum. Intensity: 2.0 (0.7, 5.3) 12 1.2 (0.5, 2.6) 14 Max. Prob.: 5.1 ----- 5 0.7 (0.2, 2.2) 6 Max intensity: 2.4 (0.8, 7.1) 10 1.1 (0.3, 3.9) 6 Cum. Intensity: 1.5 (0.6, 3.8) 13 2.0 (0.7, 5.5) 11 Max. Prob. 2.1 (0.7, 6.5) 9 1.3 --- 5		
Diot 2002[¶,*] 80 cases 160 controls 1998-2000	TCE Aromatic solvents	13 6 7 11 7 4	OR=2.39 (1.04, 5.22) All OR=2.10 (0.65, 6.75) Women OR=4.67 (0.99, 21.9) Men OR=2.67 (1.06, 6.75) All OR=2.48 (0.80, 7.70) Women OR=3.62 (0.64, 20.4) Men		High Final cumulative exposure TCE (all): OR=7.58 (1.54, 37.4) 7 cases Aromatic solvents (all): OR=3.16 (0.87, 11.6) 6 cases
Garabrant 2003[¶,¥] 660 female cases 2,227 female controls 1980-1992	TCE PCE Dry Cleaning work Benzene	8 4 7 5 31 13 3	OR=2.0 (0.8, 4.8) self-reported exposure OR=1.9 (0.6, 6.6) confirmed by expert review OR=1.4 (0.6, 3.4) self-reported exposure OR=1.1 (0.4, 2.9) confirmed by expert review OR=1.4 (0.9, 2.2) self-reported job OR=1.5 (0.8, 2.9) self-reported exposure OR=0.8 (0.2, 2.6) confirmed by expert review		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Marie 2014+ 100 cases 300 controls 2005-2008	TCE	12 8 4	OR=2.26 (0.95, 5.26) All OR=2.77 (0.80, 9.35) Men OR=1.36 (0.30, 5.04) Women		High Final cumulative exposure TCE (all): OR=3.63 (1.15, 12.1) 8 cases
	Aromatic solvents	10 2 8	OR=8.17 (2.29, 36.5) All OR=2.05 (0.60, 19.2) Men OR=26.4 (3.45, 1183) Women		High Final cumulative exposure Aromatic solvents (all): OR=7.40 (1.65, 45.3) 7 cases

* Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.

¶ Included in the Cooper et al. 2009 meta-analysis.

+ Included in the Zhao et al. 2016 meta-analysis for TCE.

¥ Included in the Zhao et al. 2016 meta-analysis for PCE and benzene.

§ Included in the Zhao et al. 2016 meta-analysis for benzene.

£ The Nietert et al. 1998 article did not report the analysis of any exposure to TCE. The authors provided this analysis to the EPA for its meta-analysis and is reported in Cooper et al. 2009.

RR: Risk Ratio
OR: Odds Ratio
SMR: Standardized Mortality Ratio
SIR: Standardized Incidence Ratio
95% CI: 95% Confidence Interval
sRR: Summary Risk Ratio
HRs: Hazard Ratio
JEM: Job-exposure matrix
I: Incidence; M: mortality
VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)

Note: The Nietert et al. 1998, Diot et al. 2002, and Marie et al. 2014 studies were included in the Zhao et al 2016 meta-analysis and are included in the table because they provide additional information on cumulative exposure and/or intensity of exposure. The Garabrant et al. 2003 study also was included in the Zhao et al 2016 meta-analysis and is included in the table to distinguish results based on self-reported exposures and results based on a review of the self-reported information by an expert in occupational/environmental exposure assessment who was blinded to case and control status.

Note: the cluster investigation by Thompson and Pope 2002 and the study by Goldman 1996 are not included in the table because of serious limitations in these studies which made them uninformative for this assessment. These limitations are discussed below.

Summary of EPA Assessment of TCE and Scleroderma

"The human and animal studies of TCE and immune-related effects provide strong evidence for a role of TCE in autoimmune disease..." "The relation between systemic autoimmune diseases, such as scleroderma, and occupational exposure to TCE has been reported in several recent studies." "...The human data, at this time, do not allow for the determination of whether the difference in effect estimates between men and women reflects the relatively low background risk of scleroderma in men, gender-related differences in exposure prevalence or in the reliability of exposure assessment (Messing et al., 2003), a gender-related difference in susceptibility to the effects of TCE, or chance." (EPA 2011)

"Strong evidence, based on multiple human and experimental animal studies, that TCE exposure causes autoimmune diseases, including scleroderma" (Chiu et al. 2013).

ATSDR Assessment

In the assessment of the evidence for causation, ATSDR placed high weight on the assessment conducted by EPA. High weight was also given to toxicological evidence from animal studies including mechanism information. The assessment also took special note of evidence from one epidemiological study of a possible susceptible population. Our assessment of the epidemiological evidence considered some of the viewpoints associated with Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if ≤1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding.

TCE

A recent meta-analysis of TCE and scleroderma included the four case-control studies listed in the table (Nietert et al. 1998, Diot et al. 2002, Garabrant et al. 2003, and Marie et al. 2014) and an additional cluster investigation in Ontario, Canada based on patients of a practice with a research interest in scleroderma (Thompson and Pope, 2002). The inclusion of the cluster investigation in the meta-analysis was problematic for several reasons: (1) the focus of investigation was not on chemical exposures and the information on employment and workplace exposures was based entirely on self-report; (2) selection bias was possible because the clinic's catchment area for the scleroderma cases (the clinic specialized in scleroderma research and cases were referred from a large area) may have been different than the clinic's catchment area for the controls who had other rheumatologic conditions; and (3) only about 3% of the cases and controls reported any exposure to TCE either at home or the workplace. The cluster investigation did not find an elevated risk for TCE. On the other hand, inclusion of the cluster investigation likely had little impact on the meta-analysis findings. The summary OR obtained by the meta-analysis was 2.07 (95% CI: 1.34, 3.17) (Zhao et al. 2016). This finding is similar to the findings

for men and women combined in the Marie et al. 2014 study (OR=2.26, 95% CI: 0.95, 5.26) and the Diot et al. 2002 study (OR=2.39, 95% CI: 1.04, 5.22).

In a previous meta-analysis conducted by EPA, which evaluated three studies listed in the table, the pooled ORs for men and women were 2.46 (95% CI: 1.13, 5.38) and 1.22 (95% CI: 0.58, 2.57), respectively (Cooper et al. 2009). The EPA researchers attempted to explain the difference in the pooled ORs for men and women: "The incidence of systemic sclerosis among men is very low (approximately 1 per 100,000 per year), and is approximately 10 times lower than the rate seen in women.... Thus, the human data, at this time, do not allow for the determination of whether the difference in effect estimates between men and women reflects the relatively low background risk of scleroderma in men, gender-related differences in exposure prevalence or in the reliability of exposure assessment..., a gender-related difference in susceptibility to the effects of TCE, or chance." (pages 4-427 and 4-428, EPA 2011). However, the difference in pooled ORs between men and women could also be partly explained by the impact of the Nietert et al. 1998 study which supplied almost two-thirds of the exposed female cases in the Cooper et al. 2009 meta-analysis. The OR for women in the Nietert et al. study was 0.70. The ORs for TCE and scleroderma among women in three other case-control studies were 2.10 (95% CI: 0.65, 6.75) (Diot et al. 2002), 2.0 (95% CI: 0.8, 4.8) (Garabrant et al. 2003), and 1.36 (95% CI: 0.30, 5.04) (Marie et al. 2014). Pooling these three odds ratios would likely result in a pooled OR between 1.7 and 2.0, still less than, but considerably closer to, the pooled OR for men observed in the EPA meta-analysis. In summary, although the Cooper et al. 2009 meta-analysis observed gender differences in the pooled ORs, much, if not most, of the difference is due to the impact of one study included in the meta-analysis.

The Nietert et al. 1998 study used a generic job-exposure matrix (JEM) that linked occupational and industrial codes to the probability and intensity of specific solvent exposure. Generic JEMs are likely to result in much greater exposure misclassification bias than industry-specific or plant-specific JEMs. Moreover, a generic JEM such as the one used in this study is likely insensitive to detect variations of exposure among women and may overestimate their exposures. These weaknesses in the use of a generic JEM to assess solvent exposures in women workers were mentioned in the Nietert et al. 1998 study.

An interesting finding in the Nietert et al. 1998 study that was not incorporated in the Cooper et al. 2009 meta-analysis or the Zhao et al. 2016 meta-analysis were the elevated ORs for both women and men exposed to TCE who tested positive for the anti-Scl-70 antibody. (The Anti-Scl-70 antibody is associated with diffuse forms of cutaneous involvement and severity of interstitial lung disease or pulmonary fibrosis.) Among women who tested positive for the anti-Scl-70 antibody, the ORs for maximum intensity, cumulative intensity, and maximum probability of exposure to TCE were 1.8, 4.0, and 2.2, respectively. Among men who tested positive, the ORs for maximum intensity, cumulative intensity, and maximum probability of exposure to TCE were 4.8. 2.6 and 5.0, respectively (Nietert et al. 1998). (Note: the study did not provide confidence intervals for this analysis.) No trend for either men or women exposed to TCE was found for those who tested negative for the anti-Scl-70 antibody. This suggests that men and women testing positive for this antibody may constitute a vulnerable subpopulation at higher risk of scleroderma from TCE exposure.

Two studies evaluated cumulative exposure to TCE and scleroderma. Both the Diot et al. 2002 study and the Marie et al. 2014 study found an increased risk among those with high cumulative exposure. In the Nietert et al. 1998 study, an increased risk was found for men in the maximum exposure intensity group as well as for men in the maximum probability of exposure group. No increased risks were found for women in the Nietert et al. 1998 study except for cumulative intensity (OR=1.2, 95% CI: 0.5, 2.6). In the Garabrant et al 2003 study, the exposure assessment based on self-reported exposures produced a similar result as the exposure assessment based on expert review of the self-reported exposures.

Animal and mechanistic information: The EPA toxicological review of TCE summarized the animal evidence for TCE exposure and autoimmune effects in animal studies: "TCE treatment induces and exacerbates autoimmune disease in genetically susceptible strains of mice, and has also been shown to induce signs of autoimmune disease in a nongenetically predisposed strain. Although the mechanism for this response is not fully understood, a number of studies have been conducted to examine this issue. The primary conclusion to date is that metabolism of the TCE to its chloral or DCA metabolites is at least partially responsible for activating T-cells or altering T-cell regulation and survival associated with polyclonal disease in susceptible mice strains." (4-424, EPA 2011)

Conclusion: Based on its review of the literature, EPA concluded that there is "Strong evidence, based on multiple human and experimental animal studies, that TCE exposure causes autoimmune diseases, including scleroderma" (Chiu 2013). ATSDR concurs with EPA's assessment. It is our conclusion that the epidemiological evidence, combined with the evidence from animal studies, provides support for a causal association between TCE exposure and scleroderma. Although the observed gender differences in the magnitude of the effect estimates adds some uncertainty, elevated risks have been observed in both women and men. Moreover, both men and women who tested positive for the anti-Scl-70 antibody and were exposed to TCE had elevated risks. The identification of a possible susceptible population adds to the evidence for causality. Although the combined human and animal evidence may not be sufficient to conclude with certainty that a causal relationship exists, it is sufficiently strong to conclude that the evidence for causality is above equipoise. Therefore, ATSDR concludes that that there is **equipoise and above evidence for causation for TCE and systemic sclerosis/scleroderma.**

PCE

The Zhao et al. 2016 meta-analysis obtained a summary OR of 2.03 (95% CI: 0.44, 9.27) for PCE and scleroderma based on three studies. One of the studies was the cluster investigation mentioned above that was based on patients of a rheumatology outpatient practice with a research interest in scleroderma (Thompson and Pope, 2002). This study had serious limitations mentioned above. A second study was also based on patients from a rheumatology practice and the exposure assessment was based primarily on self-reports (Goldman 1996). The author stated that there was no attempt at blinding the clinical examinations of cases of scleroderma and controls of other connective tissue diseases. There were 33 scleroderma cases and 246 controls. Of the 33 cases, 30 were women and four of the women reported employment in dry cleaning establishments compared to 2 women out of 210 female controls (OR and 95% CI calculated from data in the tables by ATSDR: OR=16.0, 95% CI: 2.7, 127). Of the four

scleroderma cases that reported employment in dry cleaning establishments, 3 reported PCE exposure. Both controls that reported employment in dry cleaning also reported PCE exposure (OR and 95% CI calculated by ATSDR: OR=11.6, 95% CI: 1.6, 99). No male cases of scleroderma reported employment in dry cleaning or exposure to PCE. This study was severely limited by the number of exposed cases, an exposure assessment based on self-report, the possibility of information bias due to the lack of blinding, and the possibility of selection bias due to referrals to the practice.

In the Garabrant et al. 2003 study, an OR of 1.4 (95% CI: 0.6, 3.4) was obtained for women who self-reported PCE exposure and a similar OR was observed for women who self-reported dry cleaning work (OR=1.4, 95% CI: 0.9, 2.2). The OR for PCE exposure declined to 1.1 (95% CI: 0.4, 2.9) after expert review of the self-reported exposures.

Conclusion: Although three studies were included in a recent meta-analysis, only one study used appropriate methods and an expert review of exposures. Given the paucity of information, ATSDR concludes that there **is insufficient evidence to determine whether an association exists for PCE and scleroderma**. Therefore, there is **below equipoise evidence for causation for PCE and scleroderma.**

Benzene

The Zhao et al. 2016 meta-analysis included three studies, Nietert et al. 1998, Garabrant et al. 2003, and the cluster investigation mentioned above (Thompson and Pope 2002) and obtained a summary odds ratio near the null. The cluster investigation had severe limitations for the reasons stated above. The Nietert et al. 1998 study found elevated odds ratios for both sexes but much higher for men than for women. The Garabrant et al. 2003 study included only female cases and did not find an excess risk after expert review of the self-reported information on occupational exposures.

Conclusion: Given the paucity of epidemiological evidence and the lack of supporting animal or mechanistic information, ATSDR concludes that the **evidence is insufficient to determine whether an association exists for benzene and scleroderma**. Therefore ATSDR concludes that there is **below equipoise evidence for causation for benzene and scleroderma**.

Major cardiac birth defects

Reference, type of cancer data, total # of subjects, follow-up period	Exposure[a] (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Gilboa 2012 2,047 cases 2,951 controls 1997-2002	Occupational exposure (JEM) TCE PCE Chlorinated solvents	69 82 22 10	TCE: 1.06 (0.77, 1.45), all heart defects[#] PCE: 1.10 (0.82, 1.47), all heart defects[#] Any chlorinated solvent exposure: 1.2 (0.8, 2.0), conotruncal heart defects 1.7 (0.9, 3.4) D-Transposition of the great arteries		
Drinking Water Studies					
Goldberg 1990 707 cases	TCE drinking water (sample data)	74	PR** = 2.58 (2.0, 3.4) for first trimester exposure		
Bove 1995 80,938 live births 75 towns in NJ 1985-1988	Drinking water (sample data) TCE > 10 ppb PCE > 5 ppb Benzene > 0 ppb	 4 8 5	 OR = 1.2 (0.5, 3.4) OR = 1.1 (0.6, 2.3) OR = 1.8 (0.7, 4.3)		
Massachusetts Dept of Health 1996 (Woburn, MA) 2,211 births 1975-1979 2,766 births E. Woburn 1975-1984	TCE Drinking water (modeled)	4 6	OR=0.40 (0.09, 1.35) ever exposed, Woburn as a whole (1975-1979) OR=1.11 (0.30, 4.16) East Woburn only, operation of contaminated wells vs post operation period (1975-1984)		
Aschengrau 2009 1,658 exposed births 2,999 unexposed births 1969-1983	Drinking water PCE >40 µg/L (modeled)	4	OR=1.1 (0.4, 3.3)		

Reference, type of cancer data, total # of subjects, follow-up period	Exposure* (exposure assessment)	# exposed cases	RR (SIR, SMR, OR) & 95% CI	Exposure Duration information	Exposure intensity/cumulative exposure information
Vapor Intrusion Study					
Forand 2012 1,440 births (TCE area 1,090 births (PCE area 1983-2000	Vapor intrusion (modeled) TCE PCE	 6 3 2 1	 RR = 2.40 (1.00-5.77) major heart defects RR = 4.91 (1.58-15.24), conotruncal heart defects RR = 2.91 (0.73-+11.65) major heart defects RR = 4.91 (0.69-34.90), conotruncal heart defects		

* Exposures were occupational unless otherwise noted. Exposure assessments were based on expert review by industrial hygienists of work/job histories obtained from interviews or plant records unless otherwise noted.

Ψ Odds ratios and confidence intervals calculated by ATSDR from data provided in Table 1 of the article.

** Prevalence ratio calculated by Bove 2002.

RR: Risk Ratio

OR: Odds Ratio

SMR: Standardized Mortality Ratio

SIR: Standardized Incidence Ratio

95% CI: 95% Confidence Interval

sRR: Summary Risk Ratio

HR: Hazard Ratio

JEM: Job-exposure matrix

I: Incidence; M: mortality

VOC: volatile organic compounds (i.e., TCE, PCE, 1,2-Dichloroethylene, vinyl chloride and benzene)

Summary of EPA Assessment of TCE and Cardiac Congenital Malformations

"Epidemiologic data provide some support for the possible relationship between maternal TCE exposure and birth defects in offspring, in particular cardiac defects." "...mechanistic studies, particularly based on the avian studies..., provide additional support for TCE-induced fetal cardiac malformation, particularly with respect to defects involving septal and valvular morphogenesis." "...The overall weight of evidence supports an effect of TCE on cardiac development." (EPA 2011)

"Strong evidence, based on weakly suggestive epidemiologic studies, limited experimental animal studies, and multiple mechanistic studies, that TCE causes fetal cardiac malformations; limited experimental evidence that oxidative metabolites, such as TCA and/or DCA, cause similar effects." (Chiu et al. 2013)

ATSDR Assessment

In the assessment of the evidence for causation, ATSDR placed high weight on an assessment conducted by EPA as well as mechanistic information from animal studies. Our assessment of the epidemiological evidence considered some of the viewpoints associated with Hill: (1) temporal relationship, (2) magnitude of the effect estimate (e.g., risk ratio, odds ratio, and standardized mortality ratio), (3) consistency of findings, (4) exposure-response relationship (although the relationship could be non-linear or non-monotonic), and (5) biological plausibility (Hill 1965). When considering the magnitude of the effect estimate, an effect estimate was considered "near the null value" if ≤1.10 and "elevated" if >1.10. Also considered were the effects of biases, in particular exposure misclassification, healthy worker effect, and confounding.

Few epidemiological studies have evaluated associations between cardiac defects and PCE, TCE, vinyl chloride or benzene. Nevertheless, two drinking water studies (Goldberg et al. 1990; Bove et al. 1995) and a vapor intrusion study (Forand et al. 2012) observed elevated effect estimates for TCE and cardiac defects and provide support for an association. Strong evidence for causation is provided by the animal and mechanistic studies. Animal studies suggest that prenatal exposure to TCE and its metabolites results in increased numbers of congenital cardiac defects. Studies of pregnant rats found an exposure-response relationship between exposure to TCE in drinking water and congenital heart defects in their offspring (Dawson et al. 1990; Johnson et al. 2003). A study of chick embryos found that exposure to TCE when the heart was developing resulted in cardiac defects (Rufer at al. 2010). Based on the combined evidence from human and animal studies, ATSDR concurs with EPA's assessment that there is **sufficient evidence for causation for TCE and cardiac defects**.

For PCE, the epidemiological evidence is limited and there is no supporting animal or mechanistic evidence. Therefore ATSDR concludes that there is **below equipoise evidence for causation for PCE and cardiac defects**.

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Appendix

Evaluation of possible confounding due to smoking and other risk factors for the studies listed in the tables

Study	Smoking	Other Risk Factors*
't Mannetje 2015	No information	
Anttila 1995	No evident confounding for TCE: SIR < 1.0 for lung cancer	
Aschengrau 1993	Smoking prevalence was similar for cases and controls	SES, medical history
Axelson 1994	No evident confounding: SIR < 1.0 for lung cancer	
Bassig 2015	Adjusted for smoking	Alcohol, BMI, SES
Blair 2003	Confounding of up to 20% possible	
Boice 2006	Adjusted for smoking	SES, hydrazine exposure
Bove 2014 (Marines)	Minimal confounding: RR=1.08 for COPD (Camp Lejeune vs Camp Pendleton)	SES, occupation
Bove 2014 (workers)	Minimal confounding: RR=1.21 for COPD, other smoking-related but not solvent-related diseases had RRs < 1.0 (Camp Lejeune vs Camp Pendleton)	SES, occupation
Brouwer 2015	Adjusted for smoking	Physical activity, BMI
Buhagen 2016	No information. SIR for lung cancer=1.2	
Calvert 2011	Some evidence of potential confounding: SMR=1.33 for COPD among "PCE only"; SMR=1.35 for lung cancer among "PCE plus"	
Carreón 2014	Minimal confounding by smoking (<10%)	
Chang 2003	No evident confounding: SIRs ≤1.0 for cancers of lung and larynx	
Chang 2005	No evident confounding: SIRs < 1.0 for smoking-related cancers	
Charbotel 2006	Adjusted for smoking	BMI, coffee consumption, medical history and treatments
Charbotel 2013	No confounding by smoking	Sexual & gynecological history, BMI, parity
Christensen 2013	Adjusted for smoking	Alcohol, coffee, SES
Cocco 2010	N/A (case-control study of multiple myeloma and NHL)	SES
Cocco 2013	N/A (case-control study of NHL)	Study location
Cohn 1994	No information	
Corbin 2011	Adjusted for smoking	SES
Costantini 2008	No information	SES
Costantini 2009	No information	
Costas 2002	Adjusted for maternal smoking	SES, breast-feeding
Feldman 2011	Adjusted for smoking	SES
Gallagher 2011	No confounding observed after adjustment	Medical history, family history of breast cancer, pregnancy history
Gennaro 2008	No information	
Gilboa 2012	Adjusted for smoking	Folic acid supplement, SES
Glass 2015	No confounding due to smoking	Alcohol, BMI, HRT, family history, parity, age at menarche, age at first birth

Study	Smoking	Other Risk Factors*
Gold 2011	N/A (case-control study of multiple myeloma, which is not related to smoking)	SES
Goldman 2012	Adjusted for smoking	Hobby exposures, head injury (Twin study)
Hansen 2013	Confounding minimal: lung cancer SIR=1.08. Urine TCA analysis is internal and not likely confounded by smoking	
Hsieh 2011	No evident confounding: SMRs < 1.0 for lung cancer	
Jacob 2007	No information	Hypertension, baseline proteinuria, SES
Krishnadasan 2007	No information (Smoking is not a strong risk factor for prostate cancer. A recent study[¥] found an RR of 1.4 for prostate cancer deaths among current smokers)	SES, physical activity, other chemicals, prostate screening, diabetes, family history, obesity
Linet 2015	Some evidence of potential confounding: RR=1.5 for lung cancer, but RRs < 1.0 for smoking-related bladder and oral cancers	
Lipworth 2011	No evident confounding: SMRs < 1.0 for smoking-related cancers	
Lynge 2006	Adjusted for smoking	Alcohol
Marie 2014	Adjusted for smoking	
Marsh 2007	No adjustment for smoking. SMRs and RRs for lung cancer were substantially less than 1.0 indicating possible confounding that would produce underestimates of the effects of vinyl chloride	Pay type (white/blue collar)
Mattei 2014	Adjusted for smoking	Asbestos, SES
McDonnell 2003	No information	
Miligi 2006	No confounding was observed for smoking	SES, disease history
Moore 2010	Smoking distribution was similar among cases and controls	BMI, hypertension
Morgan 1998	Minimal cofounding: SMR=1.10 for lung cancer in TCE subgroup	
Morton 2014	No information	
Neta 2012	No information	
Oddone 2014	Adjusted for smoking	Alcohol, BMI, SES, pregnancy history
Paulu 1999	Adjusted for smoking	SES, medical history
Peplonska 2010	No information	SES and risk factors specific to breast cancer
Pesch 2000	Adjusted for smoking	SES, study center
Raaschou-Nielsen 2003	Some evidence of possible confounding: lung cancer SIRs=1.4 males, 1.9 females (slightly lower SIRs for laryngeal cancer)	
Radican 2006, 2008	No evident confounding: RR < 1.0 for lung cancer. Internal analyses unlikely to be confounded by smoking	
Ruckart 2013	No confounding observed after adjusment	SES, pregnancy factors, Vietnam experience
Ruckart 2015	Smoking is not a risk factor for male breast cancer	Vietnam service, diseases related to male breast cancer
Ruder 2013	No information	SES
Saberi Hosnijeh 2013	Adjusted for smoking	alcohol
Santibañez 2008	Adjusted for smoking	Alcohol, SES
Santibañez 2010	Adjusted for smoking	Alcohol, SES
Scelo 2004	Adjusted for smoking	Other lung carcinogens

Study	Smoking	Other Risk Factors*
Schnatter 2012	Evaluated smoking with limited data and found none	
Seidler 2007	Adjusted for smoking	Alcohol
Selden 2011	Some evidence of potential confounding: SMR=1.32 for lung cancer among dry cleaners + laundry workers (although excess risk may be due to laundry workers rather than dry cleaning workers)	
Silver 2014	No evident confounding: SMRs < 1.0 for smoking-related diseases	
Stenehjem 2015	Adjusted for smoking	Other benzene exposures
Van der Mark 2015	Adjusted for smoking	Coffee, SES
Vaughan 1997	Adjusted for smoking	Alcohol, education
Vizcaya 2013	Adjusted for smoking	SES, occ. exposure to 8 lung carcinogens
Vlaanderen 2013	Internal analyses unlikely to be confounded by smoking	
Weiderpass 2001	No confounding by smoking was found	BMI, parity
Zhao 2005	Minimal confounding: RR=1.1 for lung cancer in high exposure group; RR < 1.1 for lung cancer deaths.	

* Risk factors in addition to age, sex, race/ethnicity, and calendar period that were either adjusted for or were evaluated and found not be confounders.

* Carter BD et al. Smoking and mortality – beyond established causes. N Engl J Med 2015;372:631-640.

Camp LeJeune estimated monthly average contaminant concentrations tables for Tarawa Terrace and Hadnot Point drinking water systems

Table 1a. Estimated Monthly Average Contaminant Concentrations in the Tarawa Terrace system, 1975 – 1985

Contaminant	Mean (µg/L)	Median (µg/L)	Range (µg/L)	# Months >MCL	# Months >100 µg/L
1975 – 1985 (132 months)					
Tetrachloroethylene	75.7	84.9	0 – 158.1	117	16
Trichloroethylene	3.1	3.5	0 – 6.6	11	0
Vinyl Chloride	5.6	6.2	0 – 12.3	117	0
1975 – 1979 (60 months)					
Tetrachloroethylene	68.3	68.2	43.8 – 94.8	60	0
Trichloroethylene	2.8	2.9	1.7 – 3.9	0	0
Vinyl Chloride	5.2	5.5	2.6 – 7.3	60	0
January 1980 – January 1985 (61 months) *					
Tetrachloroethylene	96.1	95.5	0[¥] – 158.1	57	16
Trichloroethylene	3.9	3.9	0[¥] – 6.6	11	0
Vinyl Chloride	7.0	7.0	0[¥] – 12.3	57	0

* Two contaminated wells were shut down in January 1985. Estimated monthly average tetrachloroethylene levels from February through December 1985 were <4 µg/L

[¥] One contaminated well was shut down for maintenance during 7/80 – 8/80 and 1/83 – 2/83. The other contaminated well was not in use until August 1984.

Table 1b. Estimated Monthly Average Contaminant Concentrations in the Hadnot Point system, 1975 – 1985

1975 – 1985 Contaminant	Mean (µg/L)	Median (µg/L)	Range (µg/L)	# Months >MCL	# Months >100 µg/L
Tetrachloroethylene	15.7	15.4	0 – 38.7	111	0
Trichloroethylene	358.7	365.9	0 – 783.3	122	113
Vinyl Chloride	24.0	22.2	0 – 67.3	122	0
Benzene	5.4	4.6	0 – 12.2	63	0
1975 – 1979					
Tetrachloroethylene	12.2	12.0	1.4 – 24.1	53	0
Trichloroethylene	325.1	327.7	60.6 – 546.3	60	55
Vinyl Chloride	17.3	16.5	2.3 – 33.4	60	0
Benzene	3.5	3.4	0 – 5.8	4	0
January 1980 – February 1985*					
Tetrachloroethylene	21.5	21.4	2.2 – 38.7	58	0
Trichloroethylene	449.2	446.2	42.6 – 783.3	62	58
Vinyl Chloride	34.3	35.7	4.2 – 67.3	62	0
Benzene	7.6	7.6	1.6 – 12.2	59	0

* Contaminated wells were shut down after February 1985. From March through December 1985, estimated monthly average levels of trichloroethylene, tetrachloroethylene, and vinyl chloride were <1 µg/L, and benzene was <4 µg/L.